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SEARCH REQUEST FORM

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Art Unit: 1623 Phone Number 30_____ Serial Number: 09/474,478

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(7E12)

If more than one ~~search is submitted~~, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

JAN

=> fil hcaplus

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CM1 1E01 Tel: 308-4498

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FILE LAST UPDATED: 8 Feb 2001 (20010208/ED)

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=> d all

L15 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:814345 HCAPLUS
DN 133:361913
TI Methods for inhibiting cutaneous inflammation and hyperpigmentation
IN Longley, B. Jack
PA The Trustees of Columbia University In the City of New York, USA
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K039-395
ICS C07K016-00; C12Q001-70
CC 15-3 (Immunochemistry)
Section cross-reference(s): 2, 8, 62, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000067794	A1	20001116	WO 2000-US12405	20000505 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-306143 19990506 <--
US 1999-474478 19991229 <--

AB This invention provides a method of preventing or treating in a subject contact dermatitis which comprises administering to the subject an amt. of a compd. capable of inhibiting the stem cell factor signaling pathway effective to prevent or treat contact dermatitis so as to thereby prevent or treat contact dermatitis in the subject. This invention also provides

a method of preventing or treating in a subject hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis and bronchospasm, mastocytosis, tumors which express activated kit, and conception.

ST contact dermatitis antiasthmatic antiallergic monoclonal ACK2

IT Keratins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(14, promoter of gene encoding; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(A, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(D, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(E, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(G, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(M, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Drug delivery systems
(anal; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Dermatitis
(contact; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Fats and Glyceridic oils, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(croton; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Bladder
(cystitis, interstitial; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Skin
(epidermis, interadnexal; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Neoplasm
(gastrointestinal stroma; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Skin, disease
(hyperpigmentation; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Allergy
(hypersensitivity; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Skin, disease
(hypopigmentation; methods for inhibiting cutaneous inflammation and

hyperpigmentation)
IT Drug delivery systems
(i.p.; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Respiratory tract
(inflammation; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(injections, i.m.; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(injections, i.v.; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(injections, s.c.; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(intestinal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(intralesional; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(intravesicular; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Abdomen
Ear
(irritant application to murine; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(liposomes; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Mast cell
(mastocytoma; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Allergy inhibitors
Anaphylaxis
Antiasthmatics
Asthma
Canidae
Carcinoma
Cat (Felis catus)
Contraceptives
Cosmetics
Dermatitis
Electron microscopy
Mammal (Mammalia)
Melanoma
Molecular weight distribution
Peptidomimetics
Signal transduction, biological
Sunburn
Urticaria
(methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Antibodies
Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Transgene
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(mice bearing; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(monoclonal, anti-kit, ACK2; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(nasal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Gamete and Germ cell
(neoplasm; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Promoter (genetic element)
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(of cytokeratin 14 gene; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(ophthalmic; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(oral; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(otic; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(parenterals; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Nose
(rhinitis; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Stem cell factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(signaling pathway; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT UV radiation
(skin injury from; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Olive oil
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(solvent; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Bronchi
(spasm; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Digestive tract
(stromal tumor; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(topical; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Mouse
(transgenic; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT Drug delivery systems
(transmucosal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT 9004-06-2, Elastase 97501-92-3, Chymase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT 70-34-8, Dinitrofluorobenzene
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(methods for inhibiting cutaneous inflammation and hyperpigmentation)
IT 67-64-1, Acetone, uses
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(solvent; methods for inhibiting cutaneous inflammation and hyperpigmentation)
RE.CNT 3
RE
(1) Bennett; US 5997865 A 1999 HCAPLUS
(2) Brownell; US 5911988 A 1999 HCAPLUS
(3) Ravetch; US 5877396 A 1999 HCAPLUS

=> s (us5997865 or us5911988 or us5877396)/pn

1 US5997865/PN
1 US5911988/PN
2 US5877396/PN
L16 4 (US5997865 OR US5911988 OR US5877396)/PN

=> d all tot

L16 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:393951 HCAPLUS
DN 131:31048
TI Method for treating asthma using stem cell factor (SCF) antibody
IN Brownell, Elise; Lukacs, Nicholas; Kunkel, Steven L.; Strieter, Robert M.
PA Bayer Corporation, USA; Univ. of Michigan
SO U.S., 21 pp., Cont. of U.S. Ser. No. 431,314, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K039-395
NCL 424145100
CC 15-3 (Immunochemistry)
Section cross-reference(s): 14
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5911988	A	19990615	US 1997-912541	19970818 <--

PRAI US 1995-431314 19950428
AB This invention provides pharmaceutical compns. comprising anti-SCF antibodies for the redn. of eosinophilia in the lungs of mammals. This invention also provides for methods of treating asthma and generating a murine model for asthma. Asthma model is prepd. in mice with immunization of Schistosoma mansoni egg antigen. In the invention, eosinophilia or eosinophil infiltration is also reduced by treating with anti-interleukin 4 antibodies.
ST stem cell factor antibody asthma eosinophilia; interleukin 4 monoclonal antibody eosinophil infiltration; airway inflammation SCF IL4 antibody; mouse model asthma Schistosoma egg antigen
IT Asthma
Disease models
Eosinophilia
(anti-stem cell factor antibody and anti-interleukin 4 antibody for treating asthma or eosinophilic airway inflammation)
IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(anti-stem cell factor antibody and anti-interleukin 4 antibody for treating asthma or eosinophilic airway inflammation)
IT Interleukin 4
Stem cell factor

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-stem cell factor antibody and anti-interleukin 4 antibody for treating asthma or eosinophilic airway inflammation)
IT Mouse
(asthma model; mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT Drug delivery systems
(carriers; mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT Eosinophil
(infiltration; anti-stem cell factor antibody and anti-interleukin 4 antibody for treating asthma or eosinophilic airway inflammation)
IT Respiratory tract
(inflammation, eosinophilic; anti-stem cell factor antibody and anti-interleukin 4 antibody for treating asthma or eosinophilic airway inflammation)
IT Drug delivery systems
(intra-tracheal; mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT Lung
Mammal (Mammalia)
Schistosoma mansoni
(mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT c-Kit (protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT Antigens
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; anti-stem cell factor antibody and anti-interleukin 4 antibody for treating asthma or eosinophilic airway inflammation)
IT Egg
(parasite; mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stem cell factor-targeted; mice immunized with Schistosoma mansoni egg antigen for use as asthma model)
RE.CNT 35
RE
(1) Ackerman, V; Chest 1994, V105, P687 MEDLINE
(2) Ando, A; J Clin Invest 1993, V92, P1639 HCAPLUS
(3) Anon; WO 9217505 1992 HCAPLUS
(4) Anon; Genzyme Catalog 1993, P196
(5) Bischoff; J Exp Med 1992, V175, P237 HCAPLUS
(6) Broxmeyer, H; Cancer Cells 1991, V3(12), P480 HCAPLUS
(7) Chester; Tibtech 1995, V13, P294 HCAPLUS
(8) Dastych, J; J of Immunology 1994, V152, P213 HCAPLUS
(9) Djukanovic, R; AAS 40 Update on Childhood Asthma 1993, P169 MEDLINE
(10) Durum; Fundamental Immunology 1993
(11) Dvorak, A; Int Arch Allergy Immunology 1993, V101, P247 MEDLINE
(12) Dvorak, A; J Leukocyte Biology 1993, V54, P465 MEDLINE
(13) Galli, S; Am Jour Pathobio 1993, V142(4), P965 HCAPLUS
(14) Galli, S; J Clin Invest 1993, V91, P148 MEDLINE
(15) Godfrey, S; AAS 40 Update on Childhood Asthma 1993, P109 MEDLINE
(16) Iemura, A; Am J Pathobiology 1994, V144(2), P321 HCAPLUS
(17) Kaushansky, K; Proteins:Structure, Function, and Genetics 1992, V12, P1 HCAPLUS
(18) Kinashi, T; Blood 1994, V83(4), P1033 HCAPLUS

(19) Li, M; Nouv Rev Fr Hematologie 1993, V35, P81 MEDLINE
(20) Lukacs; European Journal of Immunology 1995, V25, P245 HCAPLUS
(21) Lukacs; Journal of Leukocyte Biology 1996, V59, P13 HCAPLUS
(22) Lukacs; The Journal of Immunology 1995, V154, P5411 HCAPLUS
(23) Lukacs; The Journal of Immunology 1996, V156, P3945 HCAPLUS
(24) Lukacs; The Journal of Immunology 1997, V158, P4398 HCAPLUS
(25) Lukacs, N; Am J Respir Mol Biol 1994, V10, P526 HCAPLUS
(26) Morley, J; Trends in Phar Sci 1993, V14, P208 MEDLINE
(27) Page, C; Am Rev Respir Dis 1993, V147, PS29 MEDLINE
(28) Rottem, M; J Immunology 1993, V151, P4950 HCAPLUS
(29) Ryan, J; J Neurosci Research 1994, V37, P415 HCAPLUS
(30) Saito, H; Int Arch Allergy Immunology 1994, V103, P143 HCAPLUS
(31) Tsuura, Y; Virchows Archiv 1994, V424, P135 MEDLINE
(32) Valent, P; Immunology Today 1994
(33) Wegner; US 5324510 1994 HCAPLUS
(34) Windt, M; Asthma:Evolving Therapeutic Regimens 1991, P23
(35) Ziegler, I; J Biol Chem 1993, V268(17), P12544 HCAPLUS

L16 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:152338 HCAPLUS
DN 130:195761
TI Mice mutant for functional Fc receptors
IN Ravetch, Jeffrey V.; Takai, Toshiyuki; Sylvestre, Diana; Clynes, Raphael
PA Sloan Kettering Institute for Cancer Research, USA
SO U.S., 79 pp., Cont.-in-part of U.S. Ser. No. 52,267, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K049-00
ICS C12N015-00; G01N031-00
NCL 800002000
CC 15-3 (Immunochemistry)
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 5877396	A	19990302	US 1994-292569	19940818	<--
	WO 9528959	A1	19951102	WO 1995-US5171	19950424	
	W: AU, CA, FI, HU, JP, KR, MX, NO, NZ, RU, US					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	AU 9524619	A1	19951116	AU 1995-24619	19950424	
PRAI	US 1993-52267	19930423				
	WO 1994-US4467	19940422				
	US 1994-292569	19940818				
	WO 1995-US5171	19950424				

AB The authors disclose transgenic mice incapable of expressing functional Fc receptors. Using gene knockout methodol., the authors generated mice deficient for the common .gamma. subunit of Fc.gamma.RI, Fc.gamma.RIII, and Fc.epsilon.RI. Also disclosed are methods for identifying proinflammatory agents that depend on a functional Fc receptor methods of identifying anti-inflammatory agents.
ST mouse Fc receptor gamma subunit inflammation
IT Anti-inflammatory drugs
(Fc receptor .gamma. subunit-deficient transgenic mouse for detection of)
IT Anaphylaxis
Asthma
Edema
Hemorrhage
Neutrophil infiltration
(Fc receptor .gamma. subunit-deficient transgenic mouse with decreased inflammatory response to)
IT Immune complexes
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(Fc receptor .gamma. subunit-deficient transgenic mouse with decreased inflammatory response to)

IT Mast cell degranulation
(Fc receptor .gamma. subunit-deficient transgenic mouse with decreased response for)
IT Cytolysis
(antibody-dependent cellular cytotoxicity; Fc receptor .gamma. subunit-deficient transgenic mouse with decreased inflammatory response to)
IT Antibodies
Autoantibodies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cytotoxic; Fc receptor .gamma. subunit-deficient transgenic mouse with decreased inflammatory response to)
IT Virus vectors
(for generation of transgenic mouse with decreased Fc receptor-mediated function)
IT Mammal (Mammalia)
Mouse
Rodent
(generation and characterization of transgenic mouse deficient for common .gamma. subunit of Fc receptors)
IT Bioassay
(of anti-inflammatory and pro-inflammatory agents in transgenic mouse with decreased Fc receptor-mediated function)
IT Phagocytosis
(opsonophagocytosis; Fc receptor .gamma. subunit-deficient transgenic mouse with decreased inflammatory response to)
IT Plasmid vectors
(pFCR.gamma.P; for generation of transgenic mouse with decreased Fc receptor-mediated function)
IT Skin diseases
(rash; Fc receptor .gamma. subunit-deficient transgenic mouse with decreased inflammatory response to)
IT Fc.gamma.RI receptors
Fc.gamma.RII receptors
Fc.gamma.RIII receptors
Fc.epsilon.RI receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transgenic mouse with deficient expression of common .gamma. subunit of)
IT Inflammation
(type II; Fc receptor .gamma. subunit-deficient transgenic mouse with decreased response to)
RE.CNT 8
RE
(1) Alcaraz, G; Biochemistry 1987, V26(9), P2659
(2) Bruggemann; Proc Natl Acad Sc USA 1989, V86, P6709 MEDLINE
(3) Hahn; US 4686282 1987 HCAPLUS
(4) Kuster, H; J Biol Chem 1990, V265(11), P6448 HCAPLUS
(5) Love, P; Science 1993, V261, P918 HCAPLUS
(6) Maliszewski; US 5198342 1993 HCAPLUS
(7) Ra, C; J Biol Chem 1989, V264(26), P15323 HCAPLUS
(8) Takai; Cell 1994, V76, P519 HCAPLUS

L16 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:998381 HCAPLUS
DN 124:53743
TI Mice mutant for Fc receptors and method of treating autoimmune disease
IN Ravetch, Jeffrey V.; Takai, Toshiyuki; Sylvestre, Diana; Clynes, Raphael; Ono, Masao
PA Sloan-Kettering Institute for Cancer Research, USA
SO PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K039-00
ICS A61K039-395; C07H021-00; C12N015-09; C12N015-11; C12N015-67;

C12N015-90
CC 15-10 (Immunochemistry)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9528959	A1	19951102	WO 1995-US5171	19950424
	W: AU, CA, FI, HU, JP, KR, MX, NO, NZ, RU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5877396	A	19990302	US 1994-292569	19940818 <--
	AU 9524619	A1	19951116	AU 1995-24619	19950424
PRAI	WO 1994-US4467	19940422			
	US 1994-292569	19940818			
	US 1993-52267	19930423			
	WO 1995-US5171	19950424			

AB Disclosed herein is a non-naturally occurring non-human vertebrate animal incapable of expressing a functional Fc receptor (Fc.gamma.RI, Fc.gamma.RIIIA, or Fc.epsilon.RI) which may optionally be capable of expressing a protein which comprises a domain of a human Fc receptor, as well as DNA encoding such Fc receptor-based proteins. Also disclosed are in vivo methods for identifying proinflammatory agents that depend on a functional Fc receptor, in vivo methods for identifying proinflammatory agents that do not depend on a functional Fc receptor, and both in vivo and in vitro methods of identifying anti-inflammatory agents. Pharmaceutical compns. contg., and methods of treating inflammation with anti-inflammatory agents are also described.

ST murine Fc receptor mutant antiinflammatory screening; autoimmune disease murine human Fc receptor

IT Mast cell
(degranulation; mutant murine inable to display inflammatory response to cytotoxic antibodies for screening anti-inflammatory agent and for treating autoimmune diseases)

IT Neutrophil
(infiltration; mutant murine inable to display inflammatory response to cytotoxic antibodies for screening anti-inflammatory agent and for treating autoimmune diseases)

IT Mouse
(model; mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)

IT Anaphylaxis
Asthma
Basophil
Edema
Hemorrhage
Inflammation
Phagocytosis
(mutant murine inable to display inflammatory response to cytotoxic antibodies for screening anti-inflammatory agent and for treating autoimmune diseases)

IT Autoimmune disease
Inflammation inhibitors
(mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)

IT Immunoglobulin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FcR (Ig fragment Fc receptor), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FcR.gamma.Ia (IgG fragment Fc receptor Ia), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating

autoimmune diseases)
IT Immunoglobulin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fc.gamma.R (IgG fragment Fc receptor), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)
IT Immunoglobulin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fc.gamma.RI (IgG fragment Fc receptor I), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)
IT Immunoglobulin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fc.gamma.RIIIA (IgG fragment Fc receptor IIIA), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)
IT Immunoglobulin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fc.gamma.RIa (IgG fragment Fc receptor Ia), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)
IT Immunoglobulin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fc.epsilon.RI (IgE fragment Fc receptor I), mutant murine inable to expressing functional mutant Fc receptor and capable of expressing human Fc receptor for screening anti-inflammatory agent for treating autoimmune diseases)
IT Lymphocyte
(killer cell, lysis mediated by; mutant murine inable to display inflammatory response to cytotoxic antibodies for screening anti-inflammatory agent and for treating autoimmune diseases)
IT Skin, disease
(rash, mutant murine inable to display inflammatory response to cytotoxic antibodies for screening anti-inflammatory agent and for treating autoimmune diseases)

L16 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:990846 HCAPLUS
DN 124:28043
TI Agonist antibodies against the flk2/flt3 receptor and uses thereof
IN Bennett, Brian D.; Broz, Susan D.; Matthews, William; Zeigler, Francis C.
PA Genentech, Inc., USA
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-13
ICS C07K016-28; A61K039-395; A61K038-19
ICI A61K039-395, A61K038-19
CC 15-3 (Immunochemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9527062	A1	19951012	WO 1995-US3718	19950323
	W: CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5635388	A	19970603	US 1994-222299	19940404
	CA 2185211	AA	19951012	CA 1995-2185211	19950323

EP 754230 A1 19970122 EP 1995-914185 19950323
EP 754230 B1 19990512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 09512163 T2 19971209 JP 1995-525775 19950323
US 5997865 A 19991207 US 1995-434878 19950504 <--
PRAI US 1994-222299 19940404
WO 1995-US3718 19950323

AB Agonist antibodies are disclosed which bind to the extracellular domain of the flk2/flt3 receptor and thereby activate the intracellular kinase domain thereof. The labeled antibodies are useful as diagnostics for detecting the presence of the flk2/flt3 receptor in primitive hematopoietic cells for example. The antibodies are able to cause primitive hematopoietic cells to proliferate and/or differentiate and thereby enhance repopulation of mature blood cell lineages in a mammal which has undergone chemotherapy or radiation therapy or bone marrow transplantation. The antibodies are further useful for treating mammals which have suffered a decrease in blood cells as a consequence of disease or a hemorrhage, for example.

ST antibody flk2 flt3 receptor hematopoiesis stimulation

IT Nucleic acids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonist antibody-encoding; agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Blood corpuscle
Cell differentiation
Disease
Hematopoiesis
Hemorrhage
Radiotherapy
(agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Lymphokines and Cytokines
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Hematopoietic precursor cell
Lymphocyte
(differentiation and proliferation of; agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Hemopoietin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FLT3, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Therapeutics
(chemo-, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Hemopoietins
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hematopoietic cell growth factors KL, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hematopoietin, FLT3, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Lymphokines and Cytokines
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interleukins, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

IT Lymphokines and Cytokines
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lymphotoxin, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT Hematopoietic precursor cell
(myeloid, differentiation and proliferation of; agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT Bone marrow
(transplant, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT Lymphokines and Cytokines
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor necrosis factor, agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT Interferons
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma., agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT 147230-71-5, Flt3/flk2 receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)
IT 11096-26-7, Erythropoietin 67763-96-6, Insulin-like growth factor I 81627-83-0, M-CSF 83869-56-1, GM-CSF 143011-72-7, G-CSF
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agonist monoclonal antibodies against the flk2/flt3 receptor for enhance hematopoiesis in patients)

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L13 ANSWER 1 OF 1 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-687622 [67] WPIX
DNC C2000-209364
TI Prevention and treatment of contact dermatitis, hyperpigmentation,

cutaneous inflammation and other conditions, comprises inhibiting the stem cell factor signaling pathway.

DC B04 D16 D21
IN **LONGLEY, B J**
PA (UYCO) UNIV COLUMBIA NEW YORK
CYC 90
PI WO 2000067794 A1 20001116 (200067)* EN 72p A61K039-395
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
ADT WO 2000067794 A1 WO 2000-US12405 20000505
PRAI US 1999-474478 19991229; US 1999-306143 19990506
IC ICM A61K039-395
ICS C07K016-00; C12Q001-70
AB WO 200067794 A UPAB: 20001223
NOVELTY - Preventing or treating diseases comprises administering a compound capable of inhibiting the stem cell factor signaling pathway.

DETAILED DESCRIPTION - Preventing or treating contact dermatitis, hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis or bronchospasm, mastocytosis, urticaria, hypersensitivity, airway inflammation, interstitial cystitis or a tumor which expresses activated kit comprises administering to the subject a compound capable of inhibiting the stem cell factor signaling pathway effective to prevent or treat the conditions.

INDEPENDENT CLAIMS are also included for the following:

(1) providing contraception comprising administering a compound capable of inhibiting the cell factor signaling pathway effective to prevent conception;

(2) desensitizing a subject to an agent comprising administering to the subject, during the afferent phase of an immune response, a compound capable of inhibiting the stem cell factor signaling pathway effective to desensitize the subject;

(3) identifying a composition, compound or procedure which can produce a skin response comprising administering the compound or composition or applying the procedure to transgenic mice which express endogenous epidermal stem cell factor and analyzing the skin of the transgenic mice for a response;

(4) identifying a composition, compound or procedure which can reduce skin response in a subject comprises administering the composition or compound or applying the procedure to the transgenic mice which express endogenous epidermal stem cell factor and which had been induced to produce a skin disease and analyzing the skin to determine the reduction of the skin response;

(5) identifying a compound, composition or procedure which can reduce radiation damage to skin comprises administering the composition or compound or applying the procedure to the skin of the transgenic mice which express endogenous epidermal stem cell factor, subjecting the skin of the transgenic mice and control mice to radiation and analyzing the effects of the composition, compound or procedure on reducing skin radiation damage;

(6) a composition for treating human skin diseases comprising a compound that can treat skin diseases of the transgenic mice which express endogenous epidermal stem cell factor and a carrier, wherein the compound specifically targets the epidermal stem cell factor or its receptor.

ACTIVITY - Dermatological; antiinflammatory; antiasthmatic; antiinflammatory; antiallergic; immunosuppressive; cytostatic. No biological data is given.

MECHANISM OF ACTION - Stem cell factor signaling pathway inhibitor.

USE - The methods can be used to treat and/or prevent contact dermatitis, hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis or bronchospasm , mastocytosis, urticaria, hypersensitivity, airway inflammation e.g. rhinitis, interstitial cystitis, a tumor which expresses activated kit wherein the tumor is e.g. a gastrointestinal stromal tumor

or a germ cell tumor or radiation damage. The method may also be used to provide contraception (claimed).
Dwg.0/13

FS CPI
FA AB; DCN
MC CPI: B04-E01; B04-G01; B04-G21; B04-H16; B04-M01; B04-N04; B11-C08E2; B12-K04E; B14-C03; B14-H01; B14-K01; B14-K01A; B14-N07B; B14-N17; B14-N17C; B14-P01; B14-S06; D05-H09; D05-H11A; D05-H12; D05-H16A

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               E LONGLEY J/AU
L1           14 S E3,E4,E6,E7
L2           12 S L1 NOT KIDNEY

     FILE 'BIOSIS' ENTERED AT 08:29:07 ON 09 FEB 2001
               E LONGLEY B/AU
L3           30 S E4-E7
L4           18 S L3 AND (SCF OR SSCF OR KIT OR SKIT OR STEM CELL FACTOR)

     FILE 'MEDLINE' ENTERED AT 08:31:58 ON 09 FEB 2001
               E LONGLEY B/AU
L5           30 S E4-E5
L6           12 S L5 AND (SSCF OR SCF OR SKIT OR KIT OR STEM CELL OR (STEM CELL
L7            9 S L6 AND (A1.835. OR C17.800.)/CT
L8            2 S L6 AND (HYPERSENSITIVITY+NT OR HYPERPIGMENTATION+NT OR MELANI
L9           10 S L6 AND (SIGNAL TRANSDUCTION+NT OR CELL COMMUNICATION+NT OR RE
L10           9 S L6 AND (D8. OR ENZYME ACTIVATION+NT OR ENZYME STABILITY+NT)/C
L11          12 S L6-L10

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L12          31 DUP REM L11 L4 L2 (11 DUPLICATES REMOVED)

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=> d all tot l12


L12  ANSWER 1 OF 31  MEDLINE                              DUPLICATE 1
AN   2000117898     MEDLINE
DN   20117898
TI   Indolinone derivatives inhibit constitutively activated KIT
     mutants and kill neoplastic mast cells.
AU   Ma Y; Carter E; Wang X; Shu C; McMahon G; Longley B J
CS   Departments of Dermatology and Pathology, College of Physicians and
     Surgeons, Columbia University, New York, NY 10032, USA.
NC   RO1 AR43356 (NIAMS)
     P30 AR44535 (NIAMS)
SO   JOURNAL OF INVESTIGATIVE DERMATOLOGY, (2000 Feb) 114 (2) 392-4.
     Journal code: IHZ. ISSN: 0022-202X.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals; Cancer Journals
EM   200005
EW   20000503
AB   Mastocytosis is a neoplastic disease caused at least in part by somatic
     mutations of the c-KIT proto-oncogene resulting in constitutive
     activation of its protein product, KIT, the receptor tyrosine
     kinase for stem cell factor. KIT stimulates
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mast cell proliferation and prevents apoptosis of neoplastic mast cells. To develop potential therapies for mastocytosis we used indolinones, small molecules that inhibit tyrosine kinases. Four indolinone derivatives (SU4984, SU6663, SU6577, and SU5614) inhibited wild-type **KIT**, but variably inhibited constitutively activated **KIT** mutants. SU4984, SU6577, and SU5614 were effective against **KIT** with juxtamembrane activating mutations, whereas only SU6577 could suppress **KIT** containing either juxtamembrane or kinase domain activating mutations. Furthermore, SU4984, SU6577, and SU5614 killed neoplastic mast cells expressing a juxtamembrane-mutated **KIT**, whereas SU4984 and SU6577 killed neoplastic mast cells expressing **KIT** bearing a kinase domain mutation. These data show a direct correlation between inhibition of constitutively activated **KIT** and the death of neoplastic mast cells, and point to specific tyrosine kinase inhibitors as a potential therapy aimed directly at a cause of mastocytosis.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Gene Expression Regulation: DE, drug effects
*Indoles: PD, pharmacology
*Mast Cells: DE, drug effects
Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
Tumor Cells, Cultured

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Indoles)

L12 ANSWER 2 OF 31 MEDLINE DUPLICATE 2
AN 1999240730 MEDLINE
DN 99240730
TI Inhibition of spontaneous receptor phosphorylation by residues in a putative alpha-helix in the **KIT** intracellular juxtamembrane region.
AU Ma Y; Cunningham M E; Wang X; Ghosh I; Regan L; **Longley B J**
CS Department of Dermatology, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.
NC RO1 AR43356 (NIAMS)
AR44535 (NIAMS)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 May 7) 274 (19) 13399-402.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199908
AB **KIT** receptor kinase activity is repressed, prior to **stem cell** factor binding, by unknown structural constraints. Using site-directed mutagenesis, we examined the role of **KIT** intracellular juxtamembrane residues Met-552 through Ile-563 in controlling receptor autophosphorylation. Alanine substitution for Tyr-553, Trp-557, Val-559, or Val-560, all sitting along the hydrophobic side of an amphipathic alpha-helix (Tyr-553-Ile-563) predicted by the Chou-Fasman algorithm, resulted in substantially increased spontaneous receptor phosphorylation, revealing inhibitory roles for these residues. Alanine substitution for other residues, most of which are on the hydrophilic side of the helix, caused no or slightly increased basal receptor phosphorylation. Converting Tyr-553 or Trp-557 to phenylalanine generated slight or no elevation, respectively, in basal **KIT** phosphorylation, indicating that the phenyl ring of Tyr-553 and the hydrophobicity of Trp-557 are critical for the inhibition. Although alanine substitution for Lys-558 had no effect on receptor phosphorylation, its substitution with proline produced high spontaneous receptor phosphorylation, suggesting that the predicted alpha-helical conformation is involved in the inhibition. A synthetic peptide comprising Tyr-553 through Ile-563 showed circular dichroism spectra characteristic of alpha-helix, supporting the structural prediction. Thus, the **KIT** intracellular juxtamembrane region contains important residues which, in a putative alpha-helical conformation, exert inhibitory control on the kinase activity of ligand-unoccupied receptor.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Cell Membrane: ME, metabolism
Phosphorylation
Proto-Oncogene Protein c-kit: CH, chemistry
***Proto-Oncogene Protein c-kit: ME, metabolism**
Receptor Protein-Tyrosine Kinases: CH, chemistry
Receptor Protein-Tyrosine Kinases: ME, metabolism
Recombinant Proteins: CH, chemistry
Recombinant Proteins: ME, metabolism
Structure-Activity Relationship
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Recombinant Proteins)

L12 ANSWER 3 OF 31 MEDLINE DUPLICATE 3
AN 1999145598 MEDLINE
DN 99145598
TI Activating and dominant inactivating c-**KIT** catalytic domain mutations in distinct clinical forms of human mastocytosis.
AU **Longley B J Jr**; Metcalfe D D; Tharp M; Wang X; Tyrrell L; Lu S Z; Heitjan D; Ma Y
CS Departments of Dermatology and Pathology, Section of Dermatopathology, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA.. jack.longley@columbia.edu
NC RO1 AR 43356-01A2 (NIAMS)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Feb 16) 96 (4) 1609-14.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199905
AB Human mastocytosis is characterized by increased mast cells. It usually occurs as a sporadic disease that is often transient and limited in children and persistent or progressive in adults. The c-**KIT** protooncogene encodes **KIT**, a tyrosine kinase that is the receptor for mast cell growth factor. Because mutated **KIT** can transform cells, we examined c-**KIT** in skin lesions of 22 patients with sporadic mastocytosis and 3 patients with familial mastocytosis. All patients with adult sporadic mastocytosis had somatic c-**KIT** mutations in codon 816 causing substitution of valine for aspartate and spontaneous activation of mast cell growth factor receptor ($P = 0.0001$). A subset of four pediatric onset cases with clinically unusual disease also had codon 816 activating mutations substituting valine, tyrosine, or phenylalanine for aspartate. Typical pediatric patients lacked 816 mutations, but limited sequencing showed three of six had a novel dominant inactivating mutation substituting lysine for glutamic acid in position 839, the site of a potential salt bridge that is highly conserved in receptor tyrosine kinases. No c-**KIT** mutations were found in the entire coding region of three patients with familial mastocytosis. We conclude that c-**KIT** somatic mutations substituting valine in position 816 of **KIT** are characteristic of sporadic adult mastocytosis and may cause this disease. Similar mutations causing activation of the mast cell growth factor receptor are found in children apparently at risk for extensive or persistent disease. In contrast, typical pediatric mastocytosis patients lack these mutations and may express inactivating c-**KIT** mutations. Familial mastocytosis, however, may occur in the absence of c-**KIT** coding mutations.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adult
Amino Acid Substitution
Aspartic Acid
Catalytic Domain
Child
Child, Preschool

Infant
Infant, Newborn
***Mastocytosis: GE, genetics**
Mastocytosis: ME, metabolism
Mastocytosis: PA, pathology
Middle Age
*Point Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
Valine
RN 56-84-8 (Aspartic Acid); 7004-03-7 (Valine)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L12 ANSWER 4 OF 31 MEDLINE DUPLICATE 4
AN 1999142897 MEDLINE
DN 99142897
TI Clustering of activating mutations in c-**KIT**'s juxtamembrane coding region in canine mast cell neoplasms.
AU Ma Y; **Longley B J**; Wang X; Blount J L; Langley K; Caughey G H
CS Department of Dermatology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.
NC RO1 AR43356-01A2 (NIAMS)
AR44535 (NIAMS)
HL-24136 (NHLBI)
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1999 Feb) 112 (2) 165-70.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199904
AB The proto-oncogene c-**KIT** encodes a growth factor receptor, **KIT**, with ligand-dependent tyrosine kinase activity that is expressed by several cell types including mast cells. c-**KIT** juxtamembrane coding region mutations causing constitutive activation of **KIT** are capable of transforming cell lines and have been identified in a human mast cell line and in situ in human gastrointestinal stromal tumors, but have not been demonstrated in situ in neoplastic mast cells from any species. To determine whether c-**KIT** juxtamembrane mutations occur in the development of mast cell neoplasms, we examined canine mastocytomas, which are among the most common tumors of dogs and which often behave in a malignant fashion, unlike human solitary mastocytomas. Sequencing of c-**KIT** cDNA generated from tumor tissues removed from seven dogs revealed that three of the tumors contained a total of four mutations in an intracellular juxtamembrane coding region that is completely conserved among vertebrates. In addition, two mutations were found in three mast cell lines derived from two additional dogs. One mutation from one line matched that found in situ in one of the tumors. The second was found in two lines derived from one dog at different times, indicating that the mutation was present in situ in the animal. All five mutations cause high spontaneous tyrosine phosphorylation of **KIT**. Our study provides in situ evidence that activating c-**KIT** juxtamembrane mutations are present in, and may therefore contribute to, the pathogenesis of mast cell neoplasia. Our data also suggest an inhibitory role for the **KIT** juxtamembrane region in controlling the receptor kinase activity.
CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Base Sequence: GE, genetics
Dogs
Gene Expression Regulation: GE, genetics
Membrane Proteins: GE, genetics
Molecular Sequence Data
Point Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
RNA, Messenger: ME, metabolism
*Sarcoma, Mast-Cell: GE, genetics

***Skin Neoplasms: GE, genetics**
Stem Cell Factor: GE, genetics
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Membrane Proteins); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L12 ANSWER 5 OF 31 MEDLINE DUPLICATE 5
AN 1998252862 MEDLINE
DN 98252862
TI Murine cutaneous mastocytosis and epidermal melanocytosis induced by keratinocyte expression of transgenic **stem cell** factor.
AU Kunisada T; Lu S Z; Yoshida H; Nishikawa S; Nishikawa S; Mizoguchi M; Hayashi S; Tyrrell L; Williams D A; Wang X; **Longley B J**
CS Department of Immunology, School of Life Science, Faculty of Medicine, Tottori University, Yonago 683, Japan.
NC RO1AR3356 (NIAMS)
SP30041942 (CSAP)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1998 May 18) 187 (10) 1565-73. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199808
EW 19980802
AB The growth and differentiation of mast cells and melanocytes require **stem cell** factor (**SCF**), the ligand for the **kit** receptor tyrosine kinase. **SCF** may exist as a membrane-bound or soluble molecule. Abnormalities of the **SCF-kit** signaling pathway, with increased local concentrations of soluble **SCF**, have been implicated in the pathogenesis of the human disease cutaneous mastocytosis, but have not yet been shown to play a causal role. To investigate both the potential of **SCF** to cause mastocytosis and its role in epidermal melanocyte homeostasis, we targeted the expression of **SCF** to epidermal keratinocytes in mice with two different transgenes controlled by the human keratin 14 promoter. The transgenes contained cDNAs that either produced **SCF**, which can exist in both membrane-bound and soluble forms, or **SCF**, which remains essentially membrane bound. Murine epidermal keratinocyte expression of membrane-bound/ soluble **SCF** reproduced the phenotype of human cutaneous mastocytosis, with dermal mast cell infiltrates and epidermal hyperpigmentation, and caused the maintenance of a population of melanocytes in the interadnexal epidermis, an area where melanocytes and melanin are found in human skin but where they are not typically found in murine skin. Expression of membrane-bound **SCF** alone resulted in epidermal melanocytosis and melanin production, but did not by itself cause mastocytosis. We conclude, first, that a phenotype matching that of human mastocytosis can be produced in mice by keratinocyte overproduction of soluble **SCF**, suggesting a potential cause of this disease. Second, we conclude that keratinocyte expression of membrane-bound **SCF** results in the postnatal maintenance of epidermal melanocytes in mice. Since the resulting animals have skin that more closely approximates human skin than do normal mice, their study may be more relevant to human melanocyte biology than the study of skin of normal mice.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
DNA, Complementary: GE, genetics
Gene Expression Regulation
Gene Transfer
*Keratinocytes
Keratinocytes: PA, pathology
Keratinocytes: PH, physiology
***Mastocytosis: GE, genetics**
***Melanosis: GE, genetics**
Mice

Mice, Transgenic
Stem Cell Factor: BI, biosynthesis
***Stem Cell Factor: GE, genetics**
CN 0 (DNA, Complementary); **0 (Stem Cell Factor)**

L12 ANSWER 6 OF 31 MEDLINE DUPLICATE 6
AN 1999011107 MEDLINE
DN 99011107
TI c-**kit** mutation and osteopetrosis-like osteopathy in a patient with systemic mast cell disease.
AU Reinacher-Schick A; Petrasch S; **Longley B J**; Teschendorf C; Graeven U; Schmiegel W
CS Department of Medicine, Knappschaftskrankenhaus, Ruhr University, Bochum, Germany.. Anke.C.Reinacher@ruhr-uni-bochum.de
SO ANNALS OF HEMATOLOGY, (1998 Sep) 77 (3) 131-4.
Journal code: A2P. ISSN: 0939-5555.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199901
AB We describe the case of a 69-year-old man with systemic mastocytosis and severe osteopetrosis who carries a somatic activating mutation in the c-**kit** proto-oncogene. The patient initially presented with urticaria pigmentosa, progressing to systemic mast cell disease with severe anemia due to bone marrow involvement, chronic diarrhea, and hepatosplenomegaly. Direct sequencing using amplimers from reverse transcriptase-polymerase chain reactions (RT-PCR) from skin mast cell-derived RNA revealed a point mutation in the c-**kit** proto-oncogene at position 2468, introducing a new recognition site for the restriction endonuclease HinfI. Treatment with interferon-alpha 2a, prednisone, and erythropoietin was initiated. Subsequently, clinical symptoms improved significantly and hemoglobin levels are now stable at 13 g/dl.
CT Check Tags: Case Report; Comparative Study; Human; Male
Aged
***Mastocytosis: GE, genetics**
Mastocytosis: RA, radiography
Mutation
*Osteopetrosis: GE, genetics
Osteopetrosis: RA, radiography
***Proto-Oncogene Protein c-kit: GE, genetics**
Tomography, X-Ray Computed
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L12 ANSWER 7 OF 31 MEDLINE DUPLICATE 7
AN 97404340 MEDLINE
DN 97404340
TI Chymase cleavage of **stem cell** factor yields a bioactive, soluble product.
AU **Longley B J**; Tyrrell L; Ma Y; Williams D A; Halaban R; Langley K; Lu H S; Schechter N M
CS Department of Dermatology, Yale University School of Medicine, New Haven, CT 06520, USA.
NC AR 42931 (NIAMS)
R29 40514 (NIAMS)
P30AR41942
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Aug 19) 94 (17) 9017-21.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199711
AB **Stem cell** factor (**SCF**) is produced by stromal cells as a membrane-bound molecule, which may be proteolytically

cleaved at a site close to the membrane to produce a soluble bioactive form. The proteases producing this cleavage are unknown. In this study, we demonstrate that human mast cell chymase, a chymotrypsin-like protease, cleaves **SCF** at a novel site. Cleavage is at the peptide bond between Phe-158 and Met-159, which are encoded by exon 6 of the **SCF** gene. This cleavage results in a soluble bioactive product that is 7 amino acids shorter at the C terminus than previously identified soluble **SCF**. This research shows the identification of a physiologically relevant enzyme that specifically cleaves **SCF**. Because mast cells express the **KIT** protein, the receptor for **SCF**, and respond to **SCF** by proliferation and degranulation, this observation identifies a possible feedback loop in which chymase released from mast cell secretory granules may solubilize **SCF** bound to the membrane of surrounding stromal cells. The liberated soluble **SCF** may in turn stimulate mast cell proliferation and differentiated functions; this loop could contribute to abnormal accumulations of mast cells in the skin and hyperpigmentation at sites of chronic cutaneous inflammation.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Binding Sites
Hydrolysis
*Mast Cells: ME, metabolism
***Serine Endopeptidases: ME, metabolism**
***Stem Cell Factor: ME, metabolism**
Substrate Specificity

CN EC 3.4.21 (Serine Endopeptidases); EC 3.4.21.39 (chymase); **0 (Stem Cell Factor)**

L12 ANSWER 8 OF 31 MEDLINE DUPLICATE 8
AN 97275340 MEDLINE
DN 97275340
TI Chronically **KIT**-stimulated clonally-derived human mast cells show heterogeneity in different tissue microenvironments [see comments].
CM Comment in: J Invest Dermatol 1998 Feb;110(2):186-7
AU **Longley B J**; Tyrrell L; Lu S; Ma Y; Klump V; Murphy G F
CS Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut 06520-8059, USA.
NC P30AR41942 (NIAMS)
R29AR40514 (NIAMS)
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1997 May) 108 (5) 792-6.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199707
AB Human mast cell precursors arise in the bone marrow and circulate to different tissue microenvironments, where they develop distinct phenotypes that may be characterized by differential expression of the serine protease, chymase. The growth and development of mast cells is stimulated by mast cell growth factor, which is also known as **kit** ligand because its obligate receptor is **KIT**, the protein product of the c-**KIT** proto-oncogene. The in vivo influence of the **KIT** -**kit** ligand axis on the phenotype of human mast cells has not been determined. We used immunohistochemistry to detect in situ expression of tryptase and chymase by mast cells of a patient with urticaria pigmentosa and aggressive systemic mastocytosis, whose pathologic mast cells are clonally derived and chronically stimulated by **KIT** because they all contain the same point mutation causing constitutive activation of **KIT**. Mast cells in both spleen and skin expressed tryptase, but only in the skin did a majority of mast cells express chymase. We conclude that chronic stimulation of the **KIT**-**kit** ligand axis does not irrevocably commit mast cells to a chymase-positive or chymase-negative phenotype. These findings suggest that factors other than **kit** ligand predominate in determining mast cell phenotype.

CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Clone Cells: CY, cytology
Genetic Heterogeneity
*Mast Cells: CY, cytology
Mast Cells: DE, drug effects
Mast Cells: ME, metabolism
Mastocytosis: PA, pathology
Middle Age
Phenotype
Point Mutation
Proto-Oncogene Protein c-kit: GE, genetics
***Proto-Oncogene Protein c-kit: PD, pharmacology**
Serine Endopeptidases: BI, biosynthesis
Skin: CY, cytology
Spleen: CY, cytology
Urticaria Pigmentosa: PA, pathology
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 3.4.21 (Serine Endopeptidases); EC 3.4.21.39 (chymase); EC 3.4.21.59 (tryptase)

L12 ANSWER 9 OF 31 MEDLINE DUPLICATE 9
AN 97348959 MEDLINE
DN 97348959
TI Human skin/SCID mouse chimeras as an in vivo model for human cutaneous mast cell hyperplasia.
AU Christofidou-Solomidou M; **Longley B J**; Whitaker-Menezes D; Albelda S M; Murphy G F
CS Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, U.S.A.
NC HL 49591 (NHLBI)
CA 40358 (NCI)
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1997 Jul) 109 (1) 102-7.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199709
EW 19970903
AB Human skin xenografted to mice with severe combined immunodeficiency syndrome (SCID) was evaluated to determine the integrity and fate of human dermal mast cells. There was an approximately 3-fold increase in number of dermal mast cells by 3 mo after engraftment ($p < 0.05$). These cells were responsive to conventional mast cell secretagogues and were confirmed to be of human origin by ultrastructural characterization of granule substructure and by reactivity for the human mast cell proteinase, chymase. CD1a+ Langerhans cells, also bone marrow-derived cells, failed to show evidence of concomitant hyperplasia, and increased mast cell number was not associated with alterations in number of dermal vascular profiles identified immunohistochemically for human CD31. RT-PCR analysis demonstrated human but not murine **stem cell** factor (**SCF**; also termed mast cell growth factor, c-**kit** ligand) mRNA in xenografts. Epidermal reactivity for **stem cell** factor protein shifted from a cytoplasmic pattern to an intercellular pattern by 3 mo after engraftment, suggesting a secretory phenotype, as previously documented for human cutaneous mastocytosis. The majority (>90%) of mast cells demonstrated membrane reactivity for human **SCF** at the time points of peak hyperplasia. These data establish SCID mouse recipients of human skin xenografts as a potential in vivo model for cutaneous mast cell hyperplasia.
CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
Cell Degranulation
*Disease Models, Animal
Mast Cells: CY, cytology
Mast Cells: ME, metabolism
***Mastocytosis: PP, physiopathology**
Mice

*Mice, SCID: GE, genetics
Polymerase Chain Reaction
*Skin Transplantation
Stem Cell Factor: BI, biosynthesis
Stem Cell Factor: IM, immunology
*Transplantation Chimera: PH, physiology
*Transplantation, Heterologous: PH, physiology
CN **0 (Stem Cell Factor)**

L12 ANSWER 10 OF 31 MEDLINE DUPLICATE 10
AN 96172832 MEDLINE
DN 96172832
TI Somatic c-**KIT** activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm.
AU **Longley B J**; Tyrrell L; Lu S Z; Ma Y S; Langley K; Ding T G; Duffy T; Jacobs P; Tang L H; Modlin I
CS Department of Dermatology, Yale University School of Medicine, New Haven Connecticut 06510, USA.
SO NATURE GENETICS, (1996 Mar) 12 (3) 312-4.
Journal code: BRO. ISSN: 1061-4036.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199605
AB Mastocytosis is characterized by accumulations of mast cells in various organs (1). Most cases are indolent and confined to the skin, where discrete mast cell infiltrates are associated increased epidermal melanin, a clinical picture known as urticaria pigmentosa (UP). Other forms of mastocytosis combine UP with aggressive involvement of other organs or with haemotologic abnormalities (1-4). It is not known whether all forms of mastocytosis are true neoplasms or whether some might represent reactive hyperplasias (5-7). The c-**KIT** proto-oncogene encodes a type III receptor tyrosine kinase (**KIT**) that is critical to the development and survival of mast cells and melanocytes (8-11). The ligand for **KIT** (KL) can stimulate mast cell development, proliferation, and mediator release (9,12-17), as well as melanocyte proliferation and pigment production (18-20). To determine the role of c-**KIT** in the pathogenesis of mastocytosis, we examined tissue and cells isolated from a patient with UP and aggressive systemic mastocytosis with massive splenic involvement. We found a mutation that results in constitutive activation and expression of c-**KIT** in mast cells of both skin and spleen. This is the first in situ demonstration of an activation c-**KIT** mutation in neoplastic cells. It also demonstrates the clonal and neoplastic nature of this form of mastocytes.
CT Check Tags: Human; Male
Adult
Base Sequence
Clone Cells
DNA Primers
Immunoenzyme Techniques
*Mast Cells
***Mastocytosis: GE, genetics**
Mastocytosis: PP, physiopathology
Molecular Sequence Data
*Mutation
*Neoplasms, Connective Tissue: GE, genetics
***Proto-Oncogene Protein c-kit: GE, genetics**
Splenic Diseases: GE, genetics
***Urticaria Pigmentosa: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (DNA Primers)

L12 ANSWER 11 OF 31 MEDLINE DUPLICATE 11
AN 93226002 MEDLINE
DN 93226002

TI Altered metabolism of mast-cell growth factor (c-**kit** ligand) in cutaneous mastocytosis.

AU **Longley B J Jr**; Morganroth G S; Tyrrell L; Ding T G; Anderson D M; Williams D E; Halaban R

CS Department of Dermatology, Yale University School of Medicine, New Haven, Conn 06510..

NC 1 R29AR40514-01 (NIAMS)
5 R29CA44542-03 (NCI)

SO NEW ENGLAND JOURNAL OF MEDICINE, (1993 May 6) 328 (18) 1302-7.
Journal code: NOW. ISSN: 0028-4793.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199307

AB BACKGROUND AND METHODS. The lesions of cutaneous mastocytosis are characterized by dermal infiltrates of mast cells and may appear hyperpigmented because of the presence of increased levels of epidermal melanin. Mast-cell growth factor, the ligand for the product of the c-**kit** proto-oncogene, stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. We therefore looked for the expression of the mast-cell growth factor gene in the skin of patients with cutaneous mastocytosis using immunohistochemical techniques and the polymerase chain reaction. RESULTS. In the skin of normal subjects and those with unrelated diseases, immunoreactive mast-cell growth factor was associated with keratinocytes and scattered dermal cells, a pattern consistent with cell-bound mast-cell growth factor. In skin samples containing lesions and in clinically normal skin from patients with mastocytosis, however, mast-cell growth factor was also found free in the dermis and in the extracellular spaces between keratinocytes, suggesting the presence of a soluble form of this protein. Messenger RNA (mRNA) that can encode soluble mast-cell growth factor was present in the skin of patients as well as in that of normal control subjects. No sequence abnormalities were detected in mRNA for mast-cell growth factor from one patient. CONCLUSIONS. The altered distribution of mast-cell growth factor in the skin of patients with cutaneous mastocytosis is consistent with abnormal production of the soluble form of this factor. This abnormality is probably due to increased proteolytic processing, since it was not explained by differences in the splicing or sequence of mast-cell growth factor mRNA in the patients. Soluble mast-cell growth factor may cause the characteristic accumulation of mast cells and the hyperpigmentation of skin found in cutaneous mastocytosis. These findings suggest that some forms of mastocytosis represent reactive hyperplasia rather than mast-cell neoplasia.

CT Check Tags: Case Report; Female; Human; Male; Support, U.S. Gov't, P.H.S.
Adult
Base Sequence
Cells, Cultured
Hematopoietic Cell Growth Factors: GE, genetics
*Hematopoietic Cell Growth Factors: ME, metabolism
Infant, Newborn
Keratinocytes: ME, metabolism
Ligands
***Mastocytosis: ME, metabolism**
Mastocytosis: PA, pathology
Middle Age
Molecular Sequence Data
Oligonucleotide Probes
Polymerase Chain Reaction
RNA, Messenger: AN, analysis
***Skin: ME, metabolism**
Skin: PA, pathology

CN 0 (Hematopoietic Cell Growth Factors); 0 (Ligands); 0 (Oligonucleotide Probes); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L12 ANSWER 12 OF 31 MEDLINE

AN 1999348687 MEDLINE
DN 99348687
TI **SCF-KIT** pathway in human epidermal melanocyte homeostasis [letter].
AU **Longley B J**; Carter E L
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1999 Jul) 113 (1) 139-40. Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Letter
LA English
FS Priority Journals; Cancer Journals
EM 199910
CT Check Tags: Human
Epidermis: CY, cytology
Epidermis: PH, physiology
*Homeostasis
Melanocytes: CY, cytology
***Melanocytes: PH, physiology**
***Proto-Oncogene Protein c-kit: PH, physiology**
Signal Transduction
***Stem Cell Factor: PH, physiology**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit); 0 (Stem Cell Factor)**

L12 ANSWER 13 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:409343 BIOSIS
DN PREV200000409343
TI New approaches to therapy for mastocytosis: A case for treatment with **kit** kinase inhibitors.
AU **Longley, B. J. (1)**; Ma, Yongsheng; Carter, Eric; McMahon, Gerald
CS (1) Department of Dermatology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, Vanderbilt Clinic 15-208, New York, NY, 10031 USA
SO Hematology-Oncology Clinics of North America, (June, 2000) Vol. 14, No. 3, pp. 689-695. print.
ISSN: 0889-8588.
DT Book; General Review
LA English
SL English
CC Developmental Biology - Embryology - Pathological *25503
Pathology, General and Miscellaneous - Therapy *12512
Integumentary System - Pathology *18506
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Immunology and Immunochemistry - General; Methods *34502
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Pharmacology
IT Diseases
mastocytosis: congenital disease, integumentary system disease, treatment
IT Chemicals & Biochemicals
kit kinase inhibitors; **kit** protein
IT Alternate Indexing
Mastocytosis (MeSH)
IT Miscellaneous Descriptors
Book Chapter
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L12 ANSWER 14 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:411000 BIOSIS
DN PREV200000411000

TI A proposed classification of mastocytosis incorporating molecular genetics.
AU **Longley, B. J. (1)**; Metcalfe, Dean D.
CS (1) Department of Dermatology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, Vanderbilt Clinic 15-208, New York, NY, 10031 USA
SO Hematology-Oncology Clinics of North America, (June, 2000) Vol. 14, No. 3, pp. 697-701. print.
ISSN: 0889-8588.
DT Book; General Review
LA English
SL English
CC Developmental Biology - Embryology - Pathological *25503
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Integumentary System - Pathology *18506
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
IT Major Concepts
Medical Genetics (Allied Medical Sciences); Clinical Immunology (Human Medicine, Medical Sciences)
IT Parts, Structures, & Systems of Organisms
mast cells: immune system
IT Diseases
mastocytosis: classification, congenital disease, integumentary system disease, treatment
IT Chemicals & Biochemicals
human c-**kit** gene (Hominidae): mutation
IT Alternate Indexing
Mastocytosis (MeSH)
IT Miscellaneous Descriptors
Book Chapter
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L12 ANSWER 15 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:357104 BIOSIS
DN PREV199900357104
TI **SCF-KIT** pathway in human epidermal melanocyte homeostasis (and reply.
AU **Longley, B. Jack (1)**; Carter, Eric L.; Grichnik, James M.
CS (1) Section of Dermopathology, College of Physicians and Surgeons, Columbia University, 630 West 168 Street, VC 5-578, New York, NY, 10032 USA
SO Journal of Investigative Dermatology, (July, 1999) Vol. 113, No. 1, pp. 139-140.
ISSN: 0022-202X.
DT Letter
LA English
CC Integumentary System - General; Methods *18501
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General *10060
Metabolism - General Metabolism; Metabolic Pathways *13002
Endocrine System - General *17002
BC Hominidae 86215
Muridae 86375
IT Major Concepts
Chemical Coordination and Homeostasis; Integumentary System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
epidermis: integumentary system; melanocytes: homeostasis, integumentary system
IT Chemicals & Biochemicals
stem cell factor; KIT: activation
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); mouse (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates

L12 ANSWER 16 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:229797 BIOSIS
DN PREV199900229797
TI Transgenic mice expressing **stem cell factor** in basal keratinocytes develop postinflammatory hyperpigmentation in response to irritant and allergic contactants.
AU Carter, E. L. (1); Tigelaar, R. E.; **Longley, B. J.**
CS (1) Department of Dermatology, Columbia University, New York, NY USA
SO Journal of Investigative Dermatology, (April, 1999) Vol. 112, No. 4, pp. 539.
Meeting Info.: 60th Annual Meeting of the Society for Investigative Dermatology Chicago, Illinois, USA May 5-9, 1999
ISSN: 0022-202X.
DT Conference
LA English
CC Integumentary System - General; Methods *18501
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General *10060
Blood, Blood-Forming Organs and Body Fluids - General; Methods *15001
Immunology and Immunochemistry - General; Methods *34502
Allergy *35500
Toxicology - General; Methods and Experimental *22501
Endocrine System - General *17002
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Muridae 86375
IT Major Concepts
Allergy (Clinical Immunology, Human Medicine, Medical Sciences); Dermatology (Human Medicine, Medical Sciences)
IT Parts, Structures, & Systems of Organisms
basal keratinocyte: integumentary system; epidermis: integumentary system
IT Diseases
postinflammatory hyperpigmentation: integumentary system disease
IT Chemicals & Biochemicals
allergic contactant: allergen; irritant contactant: toxin; keratin 14 promoter; **stem cell factor**: expression
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): model, transgenic
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L12 ANSWER 17 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:122069 BIOSIS
DN PREV199800122069
TI **SCF** and c-**kit** in mastocytosis. A Pandora's box holding

more theories than proven facts (and reply.
AU Henz, Beate M. (1); **Longley, B. Jack**
CS (1) Dep. Dermatol., Free Univ. Berlin, Rudolf Virchow Hosp., Berlin Germany
SO Journal of Investigative Dermatology, (Feb., 1998) Vol. 110, No. 2, pp. 186-187.
ISSN: 0022-202X.
DT Letter
LA English
CC Integumentary System - General; Methods *18501
Endocrine System - General *17002
Pediatrics *25000
Developmental Biology - Embryology - General and Descriptive *25502
BC Hominidae 86215
IT Major Concepts
Integumentary System (Chemical Coordination and Homeostasis)
IT Diseases
mastocytosis: congenital disease, integumentary system disease
IT Chemicals & Biochemicals
c-**kit**: mutation; stem cell growth factor
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): child
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L12 ANSWER 18 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:154602 BIOSIS
DN PREV199800154602
TI Identification of the mutation Asp816Tyr in the c-**kit** receptor in an adult patient with urticaria pigmentosa from birth.
AU Worobec, A. S.; Foster, B. A.; Semere, T.; **Longley, B. J.**; Metcalfe, D. D.
CS NIH, Bethesd, MD USA
SO Journal of Allergy and Clinical Immunology, (Jan., 1998) Vol. 101, No. 1 PART 2, pp. S215.
Meeting Info.: 54th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Washington, DC, USA March 13-18, 1998 American Academy of Allergy, Asthma, and Immunology
. ISSN: 0091-6749.
DT Conference
LA English
CC Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biophysics - Molecular Properties and Macromolecules *10506
Pathology, General and Miscellaneous - Diagnostic *12504
Digestive System - Pathology *14006
Blood, Blood-Forming Organs and Body Fluids - General; Methods *15001
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Integumentary System - Pathology *18506
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Diseases
hepatosplenomegaly: digestive system disease; lymphadenopathy; osteopenia; osteosclerosis: bone disease, diffuse; systemic

mastocytosis: blood and lymphatic disease, immune system disease; urticaria pigmentosa: congenital disease, integumentary system disease
IT Chemicals & Biochemicals
c-**kit** receptor; c-**kit**: Asp816Val mutation
IT Methods & Equipment
bone marrow biopsy: diagnostic method; splenectomy: therapeutic method
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata; Chordata, Animalia
ORGN Organism Name
human (Hominidae): adult, patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L12 ANSWER 19 OF 31 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:248112 BIOSIS
DN PREV199698804241
TI The role of the c-**KIT** proto-oncogene and its ligand, mast cell growth factor, in the pathogenesis of mastocytosis.
AU Tyrrell, Lynda (1); Schechter, Norman; Langley, Keith; **Longley, B. Jack (1)**
CS (1) Dep. Dermatol., Yale Univ. Sch. Med., New Haven, CT USA
SO Journal of Investigative Dermatology, (1996) Vol. 106, No. 4, pp. 819.
Meeting Info.: Annual Meeting of the Society for Investigative Dermatology Washington, D.C., USA May 1-5, 1996
ISSN: 0022-202X.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Endocrine System - General *17002
Integumentary System - Pathology *18506
BC Hominidae *86215
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Dermatology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics
IT Miscellaneous Descriptors
MEETING ABSTRACT; URTICARIA PIGMENTOSA
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L12 ANSWER 20 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:79679 HCAPLUS
TI Ultraviolet B (UVB)-Induced COX-2 Expression in Murine Skin: An Immunohistochemical Study
AU Athar, Mohammad; An, Kathy P.; Morel, Kimberly D.; Kim, Arianna L.; Aszterbaum, Michelle; **Longley, Jack**; Epstein, Ervin H., Jr.; Bickers, David R.
CS Department of Dermatology, College of Physicians and Surgeons, New York, NY, 10032, USA
SO Biochem. Biophys. Res. Commun. (2001), 280(4), 1042-1047
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press

DT Journal
LA English
CC 8 (Radiation Biochemistry)
AB Cyclooxygenase (COX) is the rate-limiting enzyme in the prodn. of prostaglandins from arachidonic acid. This enzyme exists in at least two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and plays various physiol. roles. However, COX-2 expression is induced by a variety of agents, which include pro-inflammatory agents and mitogens. Evidence exists to indicate that increased expression of COX-2 occurs in several types of epithelial neoplasms. In this study, we show the effect of chronic exposure of murine skin to carcinogenic UVB on cutaneous COX-2 expression. SKH-1 mice were irradiated with 180 mJ/cm2 UVB daily for five days a week for periods ranging from 1 to 20 wk. Nontumor bearing skin areas of irradiated mice, skin of age-matched controls and benign papillomas and malignant tumors were assessed immunohistochem. for COX-2 expression in these mice. No epidermal staining occurred in any of the non-UVB-treated controls throughout the expt. Epidermal COX-2 expression only occurred in UVB-irradiated mice. After 1 and 5 wk of irradn., patchy epidermal staining mostly confined to the granular layer and stratum corneum was obsd. At week 9, staining intensity had increased, particularly in the granular layer. At week 13, staining was uniformly seen in all epidermal layers with particular prominence in the basal cell layer underlying areas of visible epidermal hyperplasia. It is of interest that the most intense staining was seen in the perinuclear region of keratinocytes and at the plasma membrane. At week 20, COX-2 staining was predominant in the granular layer, although in some tissue sections, the entire epidermis was pos. In benign papillomas, staining was confined to the superficial layers of the epidermis and in squamous cell carcinomas (SCCs), patchy staining in the granular and spinous layers predominated. In general, COX-2 expression was more intense in well-differentiated SCCs than in papillomas. In summary, our results indicate that COX-2 serves as an early marker of epidermal UVB exposure and its expression increases in benign papillomas and in SCCs. These results suggest that pharmacol. intervention using specific COX-2 inhibitors could have anticarcinogenic effects in UVB-induced human skin cancer. (c) 2001 Academic Press.

L12 ANSWER 21 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:185064 HCAPLUS
DN 133:103508
TI Recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells
AU Ding, Tiegang; Qiu, Bingsen; Tyrell, Lynda; **Longley, Jack**
CS Department of Dermatology, Medical College, Yale University, USA
SO Zhonghua Pifuke Zazhi (1999), 32(1), 36-39
CODEN: CHFTAJ; ISSN: 0412-4030
PB Zhongguo Yixue Kexueyuan Pifubing Yanjiuso
DT Journal
LA Chinese
CC 15-2 (Immunochemistry)
AB Objective To det. whether cytotoxic T cells could recognize the peptides encoded by specific gene of the third complementary detg. regions (CDR3). Methods The cells sepd. from two patients with cutaneous T cell lymphoma (CTCL) (SS and AR) CD4+. V.beta. 8+ malignant T cells (MTC) were used as peptide sequence detg. cells, CD8+ non-malignant T cells as killer cells or reactive cells, and transformed lymphoblastoid cells as major histocompatibility complex(MHC) antigen presenting cells. Results The idiotypic peptide from patient SS's TCR.beta. chain of MTC could stimulate tumor necrotizing factor (TNF) -.alpha. prodn. by autologous CD8+ T cells. TNF-.alpha. prodn. was not stimulated by a control peptide derived from the idiotypic region of patient AR's TCR protein of MTC. In contrast, the CD8+ T cells of patient AR responded to autologous peptide by secreting TNF-.alpha., but did not respond to other peptides derived from the control patient SS and patients with HIV infection. Conclusion Cytotoxic T cells may recognize and respond to a specific MHC class I assocd. peptide unique to individual malignant clones of lymphocytes in CTCL. The

identification of a tumor-specific epitope in this disease may permit the development of vaccines that could boost or initiate the CD8+ T cells-mediated immune response to the tumor cells.

ST cutaneous lymphoma TCR receptor peptide antigen cytotoxic T cell

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDR3 (third complementary detg. regions); recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT Histocompatibility antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class I; recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT Skin, neoplasm
(T-cell lymphoma; recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT Peptides, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(idiotypic peptide antigens; recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT Antigens
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(idiotypic peptide antigens; recognition of human cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT TCR (T cell receptors)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(of cutaneous T cell lymphoma; recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT CD8-positive T cell
Vaccines
(recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT Epitopes
(tumor-specific; recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

IT Tumor necrosis factors
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(.alpha.; recognition of cutaneous T cell lymphoma T cell receptor idiotypic peptide antigens by cytotoxic T cells)

L12 ANSWER 22 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:587404 HCAPLUS
DN 125:219098
TI The immune response to class I-associated tumor-specific cutaneous T-cell lymphoma antigens
AU Berger, Carole L.; Wang, Nanci; Christensen, Inger; **Longley, Jack**; Heald, Peter; Edelson, Richard L.
CS School Medicine, Yale University, New Haven, CT, 06510, USA
SO J. Invest. Dermatol. (1996), 107(3), 392-397
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB To det. whether the neoplastic T cells from patients with cutaneous T-cell lymphoma express tumor-specific antigens that can serve as the targets of an immune response, we took advantage of family-specific monoclonal antibodies, magnetic bead technol., and recombinant cytokines, which provided the previously precluded ability to isolate and expand populations of purified tumor and autologous CD8 cytotoxic T cells. Four patients with advanced cutaneous T-cell lymphoma had CD8 cells that specifically killed autologous tumor in a class I limited fashion. Tumor

cell cytolysis could be specifically enhanced by pre-culture with autologous .gamma.-irradiated tumor. The cytolytic T cells produced tumor necrosis factor-.alpha. in response to stimulation with autologous tumor. The presence of tumor-specific cytotoxic T cells recognizing distinctive class I assocd. mols. on cutaneous T-cell lymphoma tumor cells suggests that infiltration of early lesions by CD8 cells reflects host immunity to the neoplasm. These studies provide the foundation for the development of tumor vaccines through the use of cytotoxic T cells to isolate and characterize tumor-assocd. cutaneous T-cell lymphoma peptides.

ST T cell lymphoma antigen CTL cytolysis

IT Cytolysis
Vaccines
(immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

IT Histocompatibility antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(HLA, class I, immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

IT Skin, neoplasm
(T-cell lymphoma, inhibitors, immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

IT Lymphocyte
(T-cell, cytotoxic, immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

IT Neoplasm inhibitors
(skin T-cell lymphoma, immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

IT Lymphokines and Cytokines
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(tumor necrosis factor-.alpha., immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

IT Antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(tumor-assocd., immune response to class I-assocd. tumor-specific cutaneous T-cell lymphoma antigens)

L12 ANSWER 23 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:475338 HCAPLUS
DN 122:237228
TI Regulation of transgenic class II major histocompatibility genes in murine Langerhans cells
AU **Longley, Jack**; Ding, Tie-Gang; Levin, Ditza; Lewis, Julia; Edelson, Richard; Tigelaar, Robert; Flavell, Richard
CS School of Medicine, Yale University, New Haven, CT, 06520-8059, USA
SO J. Invest. Dermatol. (1995), 104(3), 329-34
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB I-E is a class II major histocompatibility complex mol. normally expressed by Langerhans cells. A series of transgenic mice were developed previously that carry E.alpha.d gene constructs with promoter-region deletions that cause expression of I-E by different cell types when maintained on a B6 (I-E[-]) genetic background. To study cis-acting gene sequences that regulate expression of class II proteins by Langerhans cells, we identified transgenic I-E expression by tissue immunoperoxidase staining and by epidermal cell suspension immunofluorescence cytometry. Mice with a transgene contg. 1.4 kilobase pairs (kb) of flanking sequence 5' to the E.alpha. initiation site expressed barely detectable levels of I-E on a tiny percentage of Langerhans cells, indicating that sequences promoting Langerhans cell expression of E.alpha. exist between 2.0 and 1.4 kb 5' of the E.alpha. initiation site. Removal of an addnl. 170 bp of 5' flanking sequence caused near-normal levels of expression by approx. one third of epidermal Langerhans cells, which contrasts with studies that showed minimal transgene expression by splenic dendritic cells in these

animals. Thus, sequences between 1.4 and 1.23 kb 5' of the E.alpha. initiation site decrease expression of I-E by epidermal Langerhans cells, but enable I-E expression by splenic dendritic cells. These studies identify Langerhans cell-specific regulatory sequences and genetic regions controlling major histocompatibility complex class II gene expression in Langerhans cells and splenic dendritic cells. The genetic regions identified may be particularly important because differential regulation of class II major histocompatibility complex protein synthesis by Langerhans cells and dendritic cells may be crucial to immune functions of intact animals.

ST Langerhans cell dendritic cell MHC antigen

IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of transgenic class II major histocompatibility genes in murine Langerhans cells and dendritic cells)

IT Histocompatibility antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(I-E, regulation of transgenic class II major histocompatibility genes in murine Langerhans cells and dendritic cells)

IT Skin
(Langerhans' cell, regulation of transgenic class II major histocompatibility genes in murine Langerhans cells and dendritic cells)

IT Histocompatibility antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility antigen complex), class II, regulation of transgenic class II major histocompatibility genes in murine Langerhans cells and dendritic cells)

IT Spleen
(dendritic cell, regulation of transgenic class II major histocompatibility genes in murine Langerhans cells and dendritic cells)

L12 ANSWER 24 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:390726 HCAPLUS
DN 122:152166
TI Human dermal endothelial cells express membrane-associated mast cell growth factor
AU Weiss, Rochelle R.; Whitaker-Menezes, Diana; **Longley, Jack**; Bender, Jeff; Murphy, George F.
CS School Medicine, University Pennsylvania, Philadelphia, PA, USA
SO J. Invest. Dermatol. (1995), 104(1), 101-6
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 15
AB Mast cell growth factor (MGF), a mol. that serves as a ligand for the receptor tyrosine kinase c-kit, is important in mast cell differentiation, migration, and activation. Previous studies of paraffin-embedded human skin using antibody to murine MGF and reverse transcription-polymerase chain reaction have demonstrated MGF protein and mRNA expression in keratinocytes and isolated dermal cells. The authors utilized a monoclonal antibody to human MGF to further define patterns of immunoreactivity in frozen specimens of neonatal and adult skin from normal individuals and from patients with urticaria pigmentosa. In addn. to keratinocytes and isolated dermal cells in normal and urticaria pigmentosa skin, MGF was detected in cells lining superficial and mid-dermal vessels. Co-expression of MGF and the vascular antigen CD31, and immunoelectron microscopy, identified MGF-pos. cells as endothelial cells. Patterns of endothelial MGF expression were not influenced by mast cell degranulation and endothelial E-selectin induction in vitro. By ultrastructure, unfixed specimens demonstrated MGF expression both within the endothelial cytoplasm and in assocn. with lumenal, but not ablumenal, surfaces. Specimens fixed with Nakane's soln. had diminished endothelial cytoplasmic MGF reactivity, but lumenal expression was maintained,

suggesting persistence of a membrane-assocd. reactivity. MGF mRNA was also detected in cultured dermal microvascular endothelial cells using reverse transcription-polymerase chain reaction. These data establish human dermal endothelial cells as sites of MGF prodn. and expression in human skin. Mast cell precursors must home to skin via vascular channels and differentiate in the immediate perivascular space. Thus, endothelial MGF may be an important determinant of adhesion and differentiation of mast cell progenitors expressing receptors for MGF.

ST skin endothelium mast cell growth factor

IT Newborn
(human dermal endothelial cells express membrane-assocd. mast cell growth factor)

IT Ribonucleic acids, messenger
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(human dermal endothelial cells express membrane-assocd. mast cell growth factor)

IT Skin
(dermis, human dermal endothelial cells express membrane-assocd. mast cell growth factor)

IT Blood vessel
(endothelium, human dermal endothelial cells express membrane-assocd. mast cell growth factor)

IT Hemopoietins
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(hematopoietic cell growth factors KL, human dermal endothelial cells express membrane-assocd. mast cell growth factor)

IT Skin
(keratinocyte, human dermal endothelial cells express membrane-assocd. mast cell growth factor)

IT Blood vessel
(micro-, endothelium, human dermal endothelial cells express membrane-assocd. mast cell growth factor)

L12 ANSWER 25 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:6370 HCAPLUS
DN 120:6370
TI Clonal deletion of V.beta.5+ T cells by transgenic I-E restricted to thymic medullary epithelium
AU Burkly, Linda C.; Degermann, Sylvie; **Longley, Jack**; Hagman, James; Brinster, Ralph L.; Lo, David; Flavell, Richard A.
CS Biogen, Inc., Cambridge, MA, 02142, USA
SO J. Immunol. (1993), 151(8), 3954-60
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB A variety of cell types expressing MHC class II mols. is known to function as APC in vitro. The authors employed the Ig .kappa. gene enhancer and promoter to target the class II E.alpha. gene, and thereby I-E, exclusively to B cells to address their APC function in vivo. Although transgenic I-E was expressed on B lymphocytes, the authors unexpectedly obtained I-E on thymic medullary epithelium but not macrophages and at low frequency on dendritic cells. Using these transgenic mice, the authors constructed bone marrow irradn. chimeras with I-E expressed only on medullary epithelium, in other to det. the role of this cell type in tolerance by clonal deletion in the thymus. Although it is accepted that bm-derived cells play a primary role in deletion, and thymic epithelium can delete clones to a lesser degree, the role of cortical vs. medullary thymic epithelium has not been directly dissected. The authors demonstrate that medullary epithelium alone can tolerize by partial deletion of I-E reactive V.beta.+ T cells. These results indicate a role for medullary epithelium in deletion during the later stages of thymic development, and support the notion that pos. and neg. selection of developing T cells can occur in distinct temporal and anat. compartments.

ST IE histocompatibility antigen thymus epithelium; T cell deletion thymus IE antigen
IT Mouse
(I-E histocompatibility antigen expression on thymic medullary epithelium in transgenic, T-cell clonal deletion in relation to)
IT Immune tolerance
(by T-cell clonal deletion, I-E histocompatibility antigen of thymic medullary epithelium in)
IT Immunoglobulins
RL: BIOL (Biological study)
(.kappa.-chain gene of, enhancer of, I-E histocompatibility antigen regulation by, in thymic medullary epithelium of transgenic mouse)
IT Histocompatibility antigens
RL: BIOL (Biological study)
(I-E, of thymic medullary epithelium, in T-cell clonal deletion)
IT Lymphocyte
(T-cell, I-E histocompatibility antigen-mediated clonal deletion of, medullary epithelium in)
IT Receptors
RL: BIOL (Biological study)
(TCR .alpha..beta. (T-cell antigen receptor .alpha..beta.), .beta.-chain genes for, V.beta.5 elements of, I-E histocompatibility antigen-mediated clonal deletion of T-cells expressing, thymic medullary epithelium in)
IT Antigens
RL: BIOL (Biological study)
(TCR .alpha..beta. receptors, .beta.-chain genes for, V.beta.5 elements of, I-E histocompatibility antigen-mediated clonal deletion of T-cells expressing, thymic medullary epithelium in)
IT Gene, animal
RL: BIOL (Biological study)
(Tcrb, for T-cell antigen receptor .beta.-chain, V.beta.5 elements for, I-E histocompatibility antigen-mediated clonal deletion of T-cells expressing, thymic medullary epithelium in)
IT Immunity
(cell-mediated, thymic medullary epithelium I-E histocompatibility antigen-mediated clonal deletion of T-cells in relation to)
IT Leukocyte
(dendritic cell, I-E histocompatibility antigen expression on, of transgenic mouse, Ig .kappa.-chain enhancer element regulation of)
IT Genetic element
RL: BIOL (Biological study)
(enhancer element, for Ig .kappa.-chain gene, I-E histocompatibility antigen regulation by, in thymic medullary epithelium of transgenic mouse)
IT Thymus gland
(medulla, epithelium, histocompatibility I-E antigen of, in T-cell clonal deletion)
IT Thymus gland
(thymocyte, I-E histocompatibility antigen-mediated clonal deletion of, medullary epithelium in)

L12 ANSWER 26 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:509341 HCAPLUS
DN 119:109341
TI Pigmentation and proliferation of human melanocytes and the effects of melanocyte-stimulating hormone and ultraviolet B light
AU Halaban, Ruth; Tyrrell, Lynda; **Longley, Jack**; Yarden, Yosef; Rubin, Jeffery
CS Sch. Med., Yale Univ., New Haven, CT, 06510-8059, USA
SO Ann. N. Y. Acad. Sci. (1993), 680(Melanotropic Peptides), 290-301
CODEN: ANYAA9; ISSN: 0077-8923
DT Journal; General Review
LA English
CC 2-5 (Mammalian Hormones)
Section cross-reference(s): 8

AB Effects of MSH on proliferation and differentiation of human melanocyte are described. Studies with human epidermal cells in vitro indicate that melanocytes respond directly to UVB light probably by activating the protein kinase A pathway, and that keratinocytes and fibroblasts regulate the proliferation of melanocytes mostly through release of basic FGF.
ST melanocyte proliferation pigmentation MSH UV; review melanocyte MSH UV
IT Cell proliferation
(of melanocytes of human, MSH and UV B light effects on)
IT Melanocyte
(pigmentation and proliferation of human, MSH and UV B light effects on)
IT Ultraviolet radiation
(B, pigmentation and proliferation of human melanocytes response to)
IT 9002-79-3, Melanocyte-stimulating hormone
RL: BIOL (Biological study)
(pigmentation and proliferation of human melanocytes response to)

L12 ANSWER 27 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:102135 HCAPLUS
DN 116:102135
TI Isolation, detection, and amplification of intact mRNA from dermatome strips, epidermal sheets, and sorted epidermal cells
AU **Longley, Jack**; Ding, Tie Gang; Cuono, Charles; Durden, Faith; Crooks, Carol; Hufeisen, Sandy; Eckert, Richard; Wood, Gary S.
CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SO J. Invest. Dermatol. (1991), 97(6), 974-9
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 9-11 (Biochemical Methods)
AB Three different strategies for isolating RNA from epidermal cells were compared. Starting with dermatoma sections frozen intraoperatively, epidermal sheets sepd. by Dispase, or disaggregated epidermal cells purified by fluorescence activated cell sorting (FACS), RNA was isolated with a guanidinium thiocyanate technique. Specific mRNA were detected by Northern blot anal. (involucrin, keratin 5, actin), or by reverse transcription and amplification with the polymerase chain reaction (PCR), using primers specific for keratinocyte products (keratins 1 and 14) and Langerhans cells (CD1a). MRNA's characteristic of Langerhans cells and of keratinocytes at different stages of differentiation were detected in dermatome and epidermal sheet prepns. as well as in FACS-sepd. cells. The use of snap-frozen dermatome sections allows the isolation of RNA from epidermis that has undergone minimal trauma and is very close to its in vivo state, but that includes RNA from some dermal cells. Extn. of RNA from Dispase-sepd. sheets involves slightly more manipulation of the epidermis but provides a sample free from dermal contaminants. PCR anal. of sorted epidermal cells is both sensitive and specific, but involves still greater manipulation. This final technique, however, allows the investigation of mRNA produced by small groups of epidermal cells that are still much closer to their in vivo state than if they had been cultured. By combining these techniques it is possible to det. the baseline prodn. of specific mRNA in the skin in vivo and to assign their prodn. to specific groups of cells with a sensitivity and specificity greater than any approach previously described.
ST RNA isolation epidermis
IT Ribonucleic acids, messenger
RL: BIOL (Biological study)
(isolation of, from epidermal cells, methods for)

L12 ANSWER 28 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1990:71230 HCAPLUS
DN 112:71230
TI Molecular cloning of CD1a (T6), a human epidermal dendritic cell marker related to class I MHC molecules
AU **Longley, Jack**; Kraus, Jan; Alonso, Miguel; Edelson, Richard
CS Dep. Dermatol., Yale Univ., New Haven, CT, 06510, USA

SO J. Invest. Dermatol. (1989), 92(4), 628-31
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 13, 15
AB To investigate the structure, function, and control of CD1a, a 1.6-kbp cDNA which encodes the expressed CD1a protein and includes untranslated 5' and 3' sequences and the poly(A) tail was cloned. As the protein recognized by the monoclonal antibody OKT6, CD1a is a useful marker for Langerhans cells. CD1a is found on these cells and on thymocytes, suggesting an important immunol. role for this mol. A cDNA library was constructed in lambda gt10 using mRNA from MOLT-4, a cell line that expresses the CD1a surface antigen. The library was then screened with an oligonucleotide synthesized according to a known partial sequence for CD1a, and the cDNA and its restriction fragments were cloned into pGEM for sequencing and probe prodn. Based on this sequence, the CD1a protein is predicted to consist of three extracellular domains (alpha 1-3), a hydrophobic transmembrane region, and a cytoplasmic tail. DNA 5' to the alpha-1 region may undergo alternative exon splicing. There is high sequence identity between the beta-2 microglobulin binding region of MHC I mols. and CD1a. The secondary structure predicted for CD1a is very similar to the actual structure of HLA-A2, a classical MHC I mol. The similarity includes the beta pleated sheets and alpha helices which form the antigen binding groove of the alpha-1 and alpha-2 domains. The homol. predicted between CD1a and HLA-A2 in these regions appears to exist on the level of secondary structure despite low primary nucleotide and amino acid sequence identity. The structural data and probes should facilitate studies of the function of CD1a as well as novel investigations of Langerhans cells.
ST human antigen CD1a gene cloning sequence; MHC antigen CD1a marker Langerhans cell; epidermal dendrite antigen CD1a mol marker
IT Gene and Genetic element, animal
RL: BIOL (Biological study)
(for antigen CD1a, of human, nucleotide and encoded peptide sequences of)
IT Molecular cloning
(of antigen CD1a gene, of human, in Escherichia coli)
IT Protein sequences
(of antigen CD1a, of human, complete)
IT Conformation and Conformers
(of antigens CD1a and HLA-A2 alpha domains, of human)
IT Antigens
RL: PRP (Properties); BIOL (Biological study)
(CD1a, gene for, of human, nucleotide and encoded peptide sequences of)
IT Antigens
RL: BIOL (Biological study)
(HLA-A2, antigen CD1a secondary structure homologous with, of human)
IT Thymus gland
(Langerhans' cell, antigen CD1a mol. marker for, gene for, nucleotide and encoded peptide sequences of)
IT Animal cell line
(Molt 4, gene for antigen CD1a of, nucleotide and encoded peptide sequences of, epidermal dendritic cell mol. marker in relation to)
IT Deoxyribonucleic acid sequences
(antigen CD1a-specifying, of human)
IT Antigens
RL: BIOL (Biological study)
(histocompatibility, class I, epidermal dendritic cell marker antigen CD1a related to, of human, nucleotide sequence and conformation in relation to)
IT 125006-39-5, Antigen CD 1a (human MOLT-4 cell deblocked protein moiety reduced)
RL: PRP (Properties)
(amino acid sequence of)

L12 ANSWER 29 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1989:572024 HCAPLUS
DN 111:172024
TI In situ transcription and detection of CD1a mRNA in epidermal cells: an alternative to standard in situ hybridization techniques
AU **Longley, Jack**; Merchant, Margaret Anne; Kacinski, Barry M.
CS Sch. Med., Yale Univ., New Haven, CT, 06511, USA
SO J. Invest. Dermatol. (1989), 93(3), 432-5
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 15-1 (Immunochemistry)
AB To develop methods for the investigation of mRNA transcription in rare epidermal cells, in situ transcription was used to study CD1a mRNA in isolated CD1a pos. cells. This Langerhans cell marker was chosen because it is not known which epidermal cells actually produce the CD1a protein and because there is evidence that CD1a mRNA is alternately splice, a situation which could lead to truncated or alternate protein products in CD1a surface protein neg. cells. Disaggregated epidermal cells were resolved into CD1a surface protein pos. and neg. groups by fluorescence activated cell sorting and cytocentrifuged onto glass slides. A synthetic 52 base, CD1a specific anti-sense oligomer was hybridized to CD1a gene transcripts in these cells, and radiolabeled cDNA synthesized in situ on the oligomer-primed CD1a transcripts. The labeled cDNA fragments were visualized in the cells of origin by autoradiog. Sixty-eight percent of cells expressing CD1a protein contained CD1a mRNA, as evidenced by grain counts >2 std. deviations above the mean value for similar cells carried through the same procedure with a control oligomer, or the mean value of CD1a surface protein neg. cells treated with the CD1a specific oligomer. Thus, it seems likely that the CD1a protein pos. epidermal cells use CD1a mRNA to make their own CD1a protein, and that a truncated or masked CD1a protein is not made by CD1a neg. neonatal foreskin epidermal cells. In situ transcription is simpler and faster than std. methods of in situ hybridization with prelabeled cDNA or RNA probes. Furthermore, it can be applied to the detection of any message of known sequence. The combination of cell sorting and in situ transcription can be used to localize and quantify the expression of specific mRNA by individual cells, allowing the study of rare and difficult-to-obtain cells.
ST CD1a mRNA epidermis in situ transcription
IT Antigens
RL: PROC (Process)
(CD1a, skin Langerhans cells expression of, in situ transcription in study of)
IT Skin, metabolism
(Langerhans' cell, CD1a antigen mRNA formation by, in situ transcription in study of)
IT Ribonucleic acid formation
(messenger, antigen CD1a-specifying, by skin Langerhans cells, in situ transcription in study of)

L12 ANSWER 30 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1979:452182 HCAPLUS
DN 91:52182
TI Staining properties of aldehyde fuchsin analogs
AU Buehner, Thomas S.; Nettleton, G. S.; **Longley, J. B.**
CS Dep. Anat., Univ. Louisville, Louisville, KY, 40232, USA
SO J. Histochem. Cytochem. (1979), 27(3), 782-7
CODEN: JHCYAS; ISSN: 0022-1554
DT Journal
LA English
CC 9-6 (Biochemical Methods)
AB An examn. was made of the role of the aldehyde component of aldehyde fuchsin in its staining reactions. Several aldehyde fuchsin analogs were prepd. by using different aldehydes. The staining quality of these analogs and pararosaniline-HCl was compared with that of aldehyde fuchsin prepd. with paraldehyde in the usual way. The major findings are:

aldehyde fuchsin staining of nonoxidized pancreatic B cells requires a stain prepd. with either paraldehyde or acetaldehyde; an aldehyde moiety is required for aldehyde fuchsin staining of strong tissue anions; and staining of elastic tissue with aldehyde fuchsin analogs resembles staining of strong tissue anions more than staining of nonoxidized pancreatic B cells. Possible reaction mechanisms of aldehyde fuchsin with tissue substrates are discussed.

ST aldehyde fuchsin analog staining; pancreas B cell staining aldehyde fuchsin; connective tissue staining aldehyde fuchsin; elastic tissue staining aldehyde fuchsin

IT Pancreas
(B cells of, staining of, by aldehyde fuchsins and pararosaniline)

IT Stains, biological
(aldehyde fuchsins, aldehyde component effect on)

IT Stomach
(chief cells of, staining of, by aldehyde fuchsins and pararosaniline)

IT Artery
Lung
(elastic tissue of, staining of, by aldehyde fuchsins and pararosaniline)

IT Intestine
(goblet cells of, staining of, by aldehyde fuchsins and pararosaniline)

IT Cartilage
(of trachea, staining of, by aldehyde fuchsins and pararosaniline)

IT Staining, biological
(with aldehyde fuchsin reagents, aldehyde component effect on)

IT Connective tissue
(elastic, staining of, by aldehyde fuchsins and pararosaniline)

IT 569-61-9
RL: ANST (Analytical study)
(staining with aldehydes and, aldehyde specificity for)

IT 70711-68-1
RL: ANST (Analytical study)
(staining with pararosaniline and, aldehyde specificity in relation to)

IT 70711-69-2 70711-70-5 70711-71-6 70711-72-7 70711-73-8
70711-74-9 70711-75-0 70906-18-2
RL: ANST (Analytical study)
(staining with pararosaniline and, specificity of aldehyde fuchsin reagent in relation to)

L12 ANSWER 31 OF 31 HCAPLUS COPYRIGHT 2001 ACS
AN 1978:20252 HCAPLUS
DN 88:20252
TI Molecular basis for acquired hemoglobin H. disease
AU Old, J.; **Longley, J.**; Wood, W. G.; Clegg, J. B.; Weatherall, D. J.
CS Nuffield Dep. Clin. Med., Radcliffe Infirm., Oxford, Engl.
SO Nature (London) (1977), 269(5628), 524-5
CODEN: NATUAS
DT Journal
LA English
CC 14-9 (Mammalian Pathological Biochemistry)
AB In a patient with myeloproliferative disease terminating in acute myeloblastic leukemia, in whom 95% of the blood Hb generated typical Hb H inclusions and 50-65% was Hb H, peripheral blood mRNA directed the synthesis of Hb .beta.-, but not .alpha.-, chains, owing to an almost complete absence of mRNA.alpha.. The deficiency in mRNA.alpha. apparently resulted from a defect in the .alpha.-chain gene transcription affecting both sets of haploid .alpha.-chain genes, and not from a major deletion of the .alpha.-chain genes.

ST Hb H alpha chain formation; messenger RNA Hb H disease

IT Ribonucleic acids, messenger
RL: BIOL (Biological study)
(Hb .alpha.-chain formation directed by, in Hb H disease)

IT Gene
RL: BIOL (Biological study)

(for Hb .alpha.-chain, transcription of, in Hb H disease)
IT 9034-79-1
RL: BIOL (Biological study)
(disease, Hb .alpha.-chain formation in)

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               SET COST OFF

     FILE 'MEDLINE' ENTERED AT 08:53:14 ON 09 FEB 2001
L1          1926 S STEM CELL FACTOR/CT,CN
L2        103629 S STEM CELLS+NT/CT
L3          1243 S PROTO-ONCOGENE PROTEIN C-KIT/CT,CN
L4        100775 S L1-L3 AND PY<=1999
L5          3090 S L4 AND C17.800./CT
L6          8114 S L4 AND A1.835./CT
L7           318 S L4 AND (MELANINS+NT OR MELANOCYTES+NT)/CT
L8           296 S L4 AND HYPERSENSITIVITY+NT/CT
L9            90 S L4 AND PIGMENTATION+NT/CT
L10         2454 S L1,L3 AND L4
L11          206 S L10 AND L5-L9
L12            9 S L11 AND HYPERPIGMENT?
L13            7 S L11 AND SKIN PIGMENTATION+NT/CT
L14         1292 S L10 AND (SIGNAL TRANSDUCTION+NT OR CELL COMMUNICATION+NT OR R
L15         1255 S L10 AND (D8. OR ENZYME ACTIVATION OR ENZYME STABILITY OR SUBS
L16          147 S L14,L15 AND L11
L17          146 S L12,L13,L16 NOT LONGLEY B?/AU
L18           26 S L1/MAJ AND L17
L19           51 S L3/MAJ AND L17
L20         2675 S (STEM CELL FACTOR OR PROTO-ONCOGENE PROTEIN C-KIT)/CN
L21         1636 S (STEM CELL FACTOR OR PROTO-ONCOGENE PROTEIN C-KIT)/CT
L22         1039 S L20 NOT L21
L23           60 S L22 AND L17
L24          129 S L18,L19,L23
L25           17 S L17 NOT L24
L26       309128 S C17.800./CT
L27           58 S L26/MAJ AND L24,L25
L28       149446 S (A1.835. OR MELANOCYTES+NT OR MELANINS+NT)/CT
L29           58 S L28/MAJ AND L24,L25
L30          108 S L27,L29
L31           38 S L24,L25 NOT L30
L32           12 S L30 NOT AB/FA
L33        16060 S PIGMENTATION DISORDERS+NT/CT
L34         2362 S SKIN PIGMENTATION/CT
L35           32 S (L33/MAJ OR L34/MAJ) AND L30
L36            4 S L30 AND L33,L34 NOT L35
L37           72 S L30 NOT L33-L36
L38          104 S L35,L37
L39           11 S L38 NOT AB/FA
L40            9 S L12,L13 AND L38
L41            5 S L12,L13 NOT L40
                 E MASTOCYTOSIS+ALL/CT
L42          109 S L38,L40,L41
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L42  ANSWER 1 OF 109  MEDLINE
AN   2000099681     MEDLINE
DN   20099681
TI   Derivation of melanocytes from embryonic stem cells in culture.
AU   Yamane T; Hayashi S; Mizoguchi M; Yamazaki H; Kunisada T
CS   Department of Immunology, School of Life Science, Faculty of Medicine,
     Tottori University, Yonago, Japan.
SO   DEVELOPMENTAL DYNAMICS, (1999 Dec) 216 (4-5) 450-8.
     Journal code: A9U. ISSN: 1058-8388.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
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FS Priority Journals
EM 200004
EW 20000404
AB We report that embryonic stem (ES) cells were efficiently induced to differentiate to melanocytes in vitro. When undifferentiated ES cells were cocultured with a bone marrow-derived stromal cell line, a very small but significant number of melanocytes were reproducibly generated. This process was greatly enhanced by addition of dexamethasone to the culture and strictly depended on steel factor, the ligand for the c-Kit receptor tyrosine kinase. Expression of c-Kit on the precursor cells was confirmed by using SCL/tal-1-/- ES cells, which are defective for producing hematopoietic cells, which were thus ruled out as possible sources of nonmelanogenic c-Kit-expressing cells. The morphology, reactivity to growth factors, and expression of melanogenic markers of the cells generated all indicated unequivocally that these cells were melanocytes. This culture system may provide a potent tool for the study of development and function of melanocytes.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Differentiation
Cell Line
Dexamethasone: PD, pharmacology
DNA-Binding Proteins: DF, deficiency
DNA-Binding Proteins: PH, physiology
Embryo
*Endothelin-3: PD, pharmacology
Genotype
Kidney
***Melanocytes: CY, cytology**
Melanocytes: DE, drug effects
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
***Monophenol Monooxygenase: GE, genetics**
***Proto-Oncogene Protein c-kit: GE, genetics**
Proto-Oncogene Proteins: PH, physiology
Stem Cell Factor: DF, deficiency
***Stem Cell Factor: PD, pharmacology**
***Stem Cells: CY, cytology**
Stem Cells: DE, drug effects
Stromal Cells: CY, cytology
RN 135471-20-4 (SCL protein); 50-02-2 (Dexamethasone)
CN EC 1.14.18.1 (Monophenol Monooxygenase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (DNA-Binding Proteins); 0 (Endothelin-3); 0 (Proto-Oncogene Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 2 OF 109 MEDLINE
AN 2000054949 MEDLINE
DN 20054949
TI Enhanced expression of SCF in the dermis is a prognostic factor for the regression of urticaria pigmentosa.
AU Onuma H; Matsui C; Morokashi M
CS Department of Dermatology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama-shi, Toyama 930-0194, Japan.
SO EUROPEAN JOURNAL OF DERMATOLOGY, **(1999 Dec)** 9 (8) 629-32.
Journal code: C4S. ISSN: 1167-1122.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
EW 20000305
AB Urticaria pigmentosa (UP) is a disorder of mast cell proliferation that occurs in cutaneous tissue. Most patients whose skin manifestations appear in infancy or childhood, experience a resolution of the disease by adolescence. In order to elucidate the relationship between mast cell

character and UP prognosis, we used an immunohistochemical approach to examine the expression of stem cell factor (SCF) and c-Kit in the skin of patients with UP. The results revealed intercellular SCF expression throughout the dermis in improving cases. On the other hand, in cases with a tendency to worsen, dermal SCF was recognized only partially or not at all. Regardless of the clinical course, intracellular SCF immunoreactivity of the entire epidermis increased in cases of child onset UP. The c-Kit expression of mast cells in all UP patients showed no relation to clinical features. These findings suggest that SCF in the dermis promotes the differentiation of mast cells infiltrating in UP, and might be an attractive candidate to induce the remission of UP.

CT Check Tags: Female; Human; Male
Adolescence
Adult
Immunohistochemistry
Infant
Infant, Newborn
Mast Cells: PA, pathology
Prognosis
Proto-Oncogene Protein c-kit: AN, analysis
***Skin: CH, chemistry**
***Stem Cell Factor: AN, analysis**
Urticaria Pigmentosa: ME, metabolism
***Urticaria Pigmentosa: PA, pathology**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit); 0 (Stem Cell Factor)**

L42 ANSWER 3 OF 109 MEDLINE
AN 2000051315 MEDLINE
DN 20051315
TI Age-related changes in dermal mast cell prevalence in BALB/c mice: functional importance and correlation with dermal mast cell expression of Kit.
AU Hart P H; Grimbaldeston M A; Hosszu E K; Swift G J; Noonan F P; Finlay-Jones J J
CS Department of Microbiology & Infectious Diseases, School of Medicine, Flinders University of South Australia, Australia.
NC RO1 CA53765 (NCI)
SO IMMUNOLOGY, **(1999 Nov)** 98 (3) 352-6.
Journal code: GH7. ISSN: 0019-2805.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200003
EW 20000302
AB Differences in dermal mast cell prevalence for adult mice of different strains have been reported previously. In this study, the dermal mast cell prevalence for BALB/c and C57BL/6 mice at 6 weeks of age was similar but as BALB/c mice matured from 6 to 10 weeks of age, their dermal mast cell prevalence halved. In contrast, there was no significant difference in the dermal mast cell prevalence of 6- and 10-week-old C57BL/6 mice. These differences determined the degree of susceptibility of BALB/c and C57BL/6 mice of different ages to UVB (UV radiation of wavelength 280-320 nm)-induced systemic immunosuppression. Expression of the receptor for stem cell factor, Kit protein, was examined on mast cells under conditions in which the dermal mast cell prevalence varied. A significant correlation was observed between Kit expression by mast cells from adult BALB/c, DBA/2 and C57BL/6 mice and dermal mast cell prevalence. In BALB/c mice, mast cell Kit expression decreased as the mice matured from 6 to 10 weeks of age and correlated with the reduction in dermal mast cell numbers. Kit levels on dermal mast cells from C57BL/6 mice were consistently higher than on mast cells from BALB/c mice although significant reductions in Kit were also measured with ageing from 6 to 10 weeks. We hypothesize that regardless of the extent of Kit expression, the dermal mast cell populations were maximally expanded in C57BL/6 mice. We suggest that

BALB/c mice of 6 and 10 weeks of age are useful hosts in which to quantitatively evaluate mast cell involvement in a range of functional assays involving skin.

CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Aging: GE, genetics
*Aging: IM, immunology
Analysis of Variance
Cell Count
***Dermis: IM, immunology**
Dermis: ME, metabolism
Dermis: RE, radiation effects
Image Processing, Computer-Assisted
Immunohistochemistry
Immunosuppression
*Mast Cells: IM, immunology
Mast Cells: ME, metabolism
Mast Cells: RE, radiation effects
Mice
*Mice, Inbred BALB C: IM, immunology
Mice, Inbred C57BL
Mice, Inbred DBA
***Proto-Oncogene Protein c-kit: ME, metabolism**
Species Specificity
Ultraviolet Rays: AE, adverse effects

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 4 OF 109 MEDLINE
AN 2000025528 MEDLINE
DN 20025528
TI A novel model to study the dorsolateral migration of melanoblasts.
AU Beauvais-Jouneau A; Pla P; Bernex F; Dufour S; Salamero J; Fassler R; Panthier J J; Thiery J P; Larue L
CS Developmental Genetics of Melanocytes, UMR 146 CNRS-Institut Curie, Bat. 110, 91405, Orsay, France.
SO MECHANISMS OF DEVELOPMENT, **(1999 Dec)** 89 (1-2) 3-14.
Journal code: AXF. ISSN: 0925-4773.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
EW 20000402
AB Melanocytes derived from pluripotent neural crest cells migrate initially in the dorsolateral pathway between the ectoderm and dermomyotome. To understand the role of specific proteins involved in this cell migration, we looked for a cellular model that mimics the in vivo behavior of melanoblasts, and that allows functional studies of their migration. We report here that wild-type embryonic stem (ES) cells are able to follow the ventral and dorsolateral neural crest pathways after being grafted into chicken embryos. By contrast, a mutant ES cell line deficient for beta1 integrin subunits, proteins involved in cell-extracellular interactions, had a severely impaired migratory behavior. Interestingly, ES cells deficient for Kit, the tyrosine kinase receptor for the stem cell factor (SCF), behaved similarly to wild-type ES cells. Thus, grafting mouse ES cells into chicken embryos provides a new cellular system that allows both in vitro and in vivo studies of the molecular mechanisms controlling dorsolateral migration.
CT Check Tags: Animal; Support, Non-U.S. Gov't
beta-Galactosidase: GE, genetics
beta-Galactosidase: ME, metabolism
Antigens, CD29: GE, genetics
Antigens, CD29: ME, metabolism
Binding Sites
Biological Markers
Cell Line

*Cell Movement: PH, physiology
Chick Embryo
DNA-Binding Proteins: GE, genetics
Embryonic Induction
Endothelin-3: GE, genetics
Fibronectins: ME, metabolism
Fluorescent Dyes: ME, metabolism
Gene Expression Regulation, Developmental
Intramolecular Oxidoreductases: GE, genetics
***Melanocytes: PH, physiology**
Mice
Mice, Mutant Strains
Monophenol Monooxygenase: GE, genetics
Mutation
Nervous System: CY, cytology
Nervous System: EM, embryology
Proteins: GE, genetics
***Proto-Oncogene Protein c-kit: GE, genetics**
Receptors, Endothelin: GE, genetics
Stem Cells: TR, transplantation
Transcription Factors: GE, genetics

CN EC 1.14.18.1 (Monophenol Monooxygenase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 3.2.1.23 (beta-Galactosidase); EC 5.3 (Intramolecular Oxidoreductases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (endothelin B receptor); 0 (tyrosinase-related protein); 0 (Antigens, CD29); 0 (Biological Markers); 0 (DNA-Binding Proteins); 0 (Endothelin-3); 0 (Fibronectins); 0 (Fluorescent Dyes); 0 (Mi protein); 0 (Proteins); 0 (Receptors, Endothelin); 0 (Slug protein); 0 (Transcription Factors)

L42 ANSWER 5 OF 109 MEDLINE
AN 2000002211 MEDLINE
DN 20002211
TI Recent advances in mastocytosis research. Summary of the Vienna Mastocytosis Meeting 1998.
AU Valent P; Escribano L; Parwaresch R M; Schemmel V; Schwartz L B; Sotlar K; Sperr W R; Horny H P
CS Department of Internal Medicine I, Division of Hematology and Hemostaseology, University of Vienna, Austria.
SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, **(1999 Sep)** 120 (1) 1-7. Ref: 67
Journal code: BJ7. ISSN: 1018-2438.
CY Switzerland
DT Conference; Conference Article; (CONGRESSES)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200002
EW 20000204
AB The term mastocytosis denotes a heterogenous group of disorders characterized by abnormal growth and accumulation of mast cells in one or more organs. Cutaneous and systemic variants of the disease have been described. Mast cell disorders have also been categorized according to other aspects, such as family history, age, course of disease, or presence of a concomitant myeloid neoplasm. However, so far, generally accepted disease criteria are missing. Recently, a number of diagnostic (disease-related) markers have been identified in mastocytosis research. These include the mast cell enzyme tryptase, CD2, and mast cell growth factor receptor c-kit (CD117). Several gain-of-function-mutations in the kinase domain of c-kit appear to occur in mastocytosis supporting the clonal (neoplastic) nature of the disease. Also, certain point mutations appear to be associated with distinct variants of mastocytosis, i.e. Asp-816-->Val with a subset of sporadic persistent (systemic) mastocytosis (mostly adults), and Gly-839-->Lys with (a subset of) typical pediatric (mostly cutaneous) mastocytosis. Another potential indicator of mast cell neoplasm is the T-/NK-cell-associated marker CD2. This antigen (LFA-2) is

abnormally expressed on neoplastic mast cells in cases of systemic mastocytosis or mast cell leukemia, but not found on normal mast cells. The mast cell enzyme tryptase is increasingly used as a serum- and immunohistochemical marker to estimate the actual spread of disease (burden of neoplastic mast cells). The clinical significance of novel mastocytosis markers is currently under investigation. First results indicate that they may be useful to define reliable criteria for the delineation of the disease.

CT Check Tags: Human
Adult
Antigens, CD: ME, metabolism
Bone Marrow Cells: PA, pathology
Immunohistochemistry
Mast Cells: PA, pathology
***Mastocytosis**
Mastocytosis: GE, genetics
Mastocytosis: IM, immunology
Mastocytosis: PA, pathology
Phenotype
Point Mutation
Prognosis
Proto-Oncogene Protein c-kit: GE, genetics
Serine Endopeptidases: BL, blood
Terminology

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 3.4.21 (Serine Endopeptidases); EC 3.4.21.59 (tryptase); 0 (Antigens, CD)

L42 ANSWER 6 OF 109 MEDLINE
AN 1999456789 MEDLINE
DN 99456789
TI Deficiency of Trp53 rescues the male fertility defects of Kit(W-v) mice but has no effect on the survival of melanocytes and mast cells.
AU Jordan S A; Speed R M; Jackson I J
CS MRC Human Genetics Unit, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, United Kingdom.
SO DEVELOPMENTAL BIOLOGY, **(1999 Nov 1)** 215 (1) 78-90.
Journal code: E7T. ISSN: 0012-1606.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200002
EW 20000204
AB Mutations of the receptor tyrosine kinase, Kit, or its ligand, mast growth factor (Mgf), affect three unrelated cell populations: melanocytes, germ cells, and mast cells. Kit signaling is required initially to prevent cell death in these lineages both in vitro and in vivo. Mgf appears to play a role in the survival of some hematopoietic cells in vitro by modulating the activity of p53. Signaling by Mgf inhibits p53-induced apoptosis of erythroleukemia cell lines and suppresses p53-dependent radiation-induced apoptosis of bone marrow cells. We tested the hypothesis that cell survival in Kit mutant mice would be enhanced by p53 deficiency in vivo. Double-mutant mice, which have greatly reduced Kit receptor tyrosine kinase activity and also lack Trp53, were generated and the affected cell lineages examined. Mast cell, melanoblast, and melanocyte survival in the double Kit(W-v/W-v):Trp53(-/-) mutants was not increased compared to the single Kit(W-v/W-v):Trp53(+/+) mutants. However, double-mutant males showed an increase in sperm viability and could father litters, in contrast to their homozygous Kit mutant, wild-type p53 littermates. This germ cell rescue appears to be male specific, as female ovaries were similar in mice homozygous for the Kit mutant allele with or without p53. We conclude that defective Kit signaling in vivo results in apoptosis by a p53-independent pathway in melanocyte and mast cell lineages but that in male germ cells apoptosis in the absence of Kit is p53-dependent.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't

Apoptosis
Cell Survival
Embryo: CY, cytology
Embryo: PH, physiology
*Genes, p53
Genotype
Homozygote
*Infertility, Male: GE, genetics
Infertility, Male: PP, physiopathology
*Mast Cells: CY, cytology
***Melanocytes: CY, cytology**
Mice
Mice, Inbred CBA
Mice, Inbred Strains
Mice, Knockout
Ovary: PH, physiology
Protein p53: DF, deficiency
Protein p53: GE, genetics
*Protein p53: ME, metabolism
Proto-Oncogene Protein c-kit: GE, genetics
***Proto-Oncogene Protein c-kit: PH, physiology**
Stem Cell Factor: PH, physiology
Testis: CY, cytology
Testis: PA, pathology
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Protein p53); **0 (Stem Cell Factor)**

L42 ANSWER 7 OF 109 MEDLINE
AN 1999398114 MEDLINE
DN 99398114
TI C-kit activating mutation in a neonate with in-utero presentation of systemic mastocytosis associated with myeloproliferative disorder [letter].
AU Kuint J; Bielorai B; Gilat D; Birenbaum E; Amariglio N; Rechavi G
SO BRITISH JOURNAL OF HAEMATOLOGY, **(1999 Sep)** 106 (3) 838-9.
Journal code: AXC. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Letter
LA English
FS Priority Journals; Cancer Journals
EM 200001
EW 20000104
CT Check Tags: Case Report; Human; Male
Infant
***Mastocytosis: GE, genetics**
*Mutation: GE, genetics
*Myeloproliferative Disorders: GE, genetics
***Proto-Oncogene Protein c-kit: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 8 OF 109 MEDLINE
AN 1999396707 MEDLINE
DN 99396707
TI Zebrafish sparse corresponds to an orthologue of c-kit and is required for the morphogenesis of a subpopulation of melanocytes, but is not essential for hematopoiesis or primordial germ cell development.
AU Parichy D M; Rawls J F; Pratt S J; Whitfield T T; Johnson S L
CS Department of Genetics, Washington University School of Medicine, Box 8232, St Louis, MO 63110, USA.. dparichy@genetics.wustl.edu
NC GM56988 (NIGMS)
SO DEVELOPMENT, **(1999 Aug)** 126 (15) 3425-36.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199911
AB The relative roles of the Kit receptor in promoting the migration and survival of amniote melanocytes are unresolved. We show that, in the zebrafish, Danio rerio, the pigment pattern mutation sparse corresponds to an orthologue of c-kit. This finding allows us to further elucidate morphogenetic roles for this c-kit-related gene in melanocyte morphogenesis. Our analyses of zebrafish melanocyte development demonstrate that the c-kit orthologue identified in this study is required both for normal migration and for survival of embryonic melanocytes. We also find that, in contrast to mouse, the zebrafish c-kit gene that we have identified is not essential for hematopoiesis or primordial germ cell development. These unexpected differences may reflect evolutionary divergence in c-kit functions following gene duplication events in teleosts.
CT Check Tags: Animal; Comparative Study; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Base Sequence
DNA Primers: GE, genetics
DNA, Complementary: GE, genetics
Evolution
Germ Cells: GD, growth & development
Hematopoiesis: GE, genetics
***Melanocytes: CY, cytology**
Mice
Neural Crest: CY, cytology
Phylogeny
***Proto-Oncogene Protein c-kit: GE, genetics**
Species Specificity
*Zebrafish: EM, embryology
*Zebrafish: GE, genetics
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (DNA Primers); 0 (DNA, Complementary)

L42 ANSWER 9 OF 109 MEDLINE
AN 1999299573 MEDLINE
DN 99299573
TI Genetic analysis of steel and the PG-M/versican-encoding gene AxPG as candidates for the white (d) pigmentation mutant in the salamander Ambystoma mexicanum.
AU Parichy D M; Stigson M; Voss S R
CS Section of Integrative Biology, University of Texas at Austin, Austin TX 78712-1064, USA.. dparichy@genetics.wustl.edu
NC GM53258 (NIGMS)
SO DEVELOPMENT GENES AND EVOLUTION, **(1999 Jun)** 209 (6) 349-56. Journal code: C1R. ISSN: 0949-944X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AF119044
EM 199909
EW 19990902
AB Vertebrate non-retinal pigment cells are derived from neural crest (NC) cells, and several mutations have been identified in the Mexican axolotl Ambystoma mexicanum (Ambystomatidae) that affect the development of these cell lineages. In "white" (d) mutant axolotls, premigratory NC cells differentiate as pigment cells, yet fail to disperse, survive, or both, and this leads to a nearly complete absence of pigment cells in the skin. Previous studies revealed that d affects pigment cell development non-autonomously, and have reported differences between white and wild-type axolotls in the structure and composition of the extracellular matrix through which NC and pigment cells migrate. Here we test the correspondence of d and two candidate genes: steel and AxPG. In amniotes, Steel encodes the cytokine Steel factor (mast cell growth factor; stem cell factor; kit ligand), which is expressed along the migratory pathways of melanocyte precursors and is required by these cells for their

migration and survival; mammalian Steel mutants resemble white mutant axolotls in having a deficit or complete absence of pigment cells. In contrast, AxPG encodes a PG-M/versican-like proteoglycan that may promote the migration of A. mexicanum pigment cells, and AxPG expression is reduced in white mutant axolotls. We cloned a salamander orthologue of steel and used a partial genetic linkage map of Ambystoma to determine the genomic locations of steel, AxPG, and d. We show that the three genes map to different linkage groups, excluding steel and AxPG as candidates for d.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Ambystoma mexicanum: EM, embryology
*Ambystoma mexicanum: GE, genetics
Amino Acid Sequence
Chromosome Mapping
Cloning, Molecular
DNA, Complementary: CH, chemistry
DNA, Complementary: GE, genetics
Gene Expression Regulation, Developmental
Molecular Sequence Data
Mutation
*Proteochondroitin Sulfates: GE, genetics
Sequence Alignment
Sequence Analysis, DNA
Sequence Homology, Amino Acid
***Skin Pigmentation: GE, genetics**
***Stem Cell Factor: GE, genetics**

RN 126968-45-4 (versican)
CN 0 (DNA, Complementary); 0 (Proteochondroitin Sulfates); **0 (Stem Cell Factor)**

L42 ANSWER 10 OF 109 MEDLINE
AN 1999294709 MEDLINE
DN 99294709
TI Altered cell-surface targeting of stem cell factor causes loss of melanocyte precursors in Steel17H mutant mice.
AU Wehrle-Haller B; Weston J A
CS Department of Pathology, Centre Medical Universitaire, 1, Rue Michel-Servet, Geneva 4, 1211, Switzerland.. Bernhard.Wehrle-Haller@medecine.unige.ch
NC DE-04316 (NIDCR)
SO DEVELOPMENTAL BIOLOGY, **(1999 Jun 1)** 210 (1) 71-86.
Journal code: E7T. ISSN: 0012-1606.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199909
AB The normal products of the murine Steel (Sl) and Dominant white spotting (W) genes are essential for the development of melanocyte precursors, germ cells, and hematopoietic cells. The Sl locus encodes stem cell factor (SCF), which is the ligand of c-kit, a receptor tyrosine kinase encoded by the W locus. One allele of the Sl mutation, Sl17H, exhibits minor hematopoietic defects, sterility only in males, and a complete absence of coat pigmentation. The Sl17H gene encodes SCF protein which exhibits an altered cytoplasmic domain due to a splicing defect. In this paper we analyzed the mechanism by which the pigmentation phenotype in Sl17H mutant mice occurs. We show that in embryos homozygous for Sl17H the number of melanocyte precursors is severely reduced on the lateral neural crest migration pathway by e11.5 and can no longer be detected by e13.5 when they would enter the epidermis in wildtype embryos. The reduced number of dispersing melanocyte precursors correlates with a reduction of SCF immunoreactivity in mutant embryos in all tissues examined. Regardless of the reduced amount, functional SCF is present at the cell surface of fibroblasts transfected with Sl17H mutant SCF cDNA. Since SCF immunoreactivity normally accumulates in basolateral compartments of SCF-expressing embryonic epithelial tissues, we analyzed the localization

of wildtype and Sl17H mutant SCF protein in transfected epithelial (MDCK) cells in vitro. As expected, wildtype forms of SCF localize to and are secreted from the basolateral compartment. In contrast, mutant forms of SCF, which either lack a membrane anchor or exhibit the Sl17H altered cytoplasmic tail, localize to and are secreted from the apical compartment of the cultured epithelium. We suggest, therefore, that the loss of melanocyte precursors prior to epidermal invasion, and the loss of germ cells from mature testis, can be explained by the inability of Sl17H mutant SCF to be targeted to the basolateral compartment of polarized epithelial keratinocytes and Sertoli cells, respectively. Copyright 1999 Academic Press.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Biotinylation
Cell Adhesion
Cell Line
Cell Movement
Embryo: ME, metabolism
Gene Expression Regulation, Developmental
Immunohistochemistry
In Situ Hybridization
Intramolecular Oxidoreductases: GE, genetics
***Melanocytes: ME, metabolism**
Mice
Mutation
Neural Crest: EM, embryology
Pigmentation: GE, genetics
Proto-Oncogene Protein c-kit: GE, genetics
RNA, Messenger: GE, genetics
***Stem Cell Factor: GE, genetics**
Stem Cell Factor: ME, metabolism
Transfection

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 5.3 (Intramolecular Oxidoreductases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L42 ANSWER 11 OF 109 MEDLINE
AN 1999282275 MEDLINE
DN 99282275
TI Analysis of c-kit exon 11 and exon 17 of urticaria pigmentosa that occurred in monozygotic twin sisters.
AU Sato-Matsumura K C; Matsumura T; Koizumi H; Sato H; Nagashima K; Ohkawara A
CS Department of Dermatology, Hokkaido University School of Medicine, Sapporo, Japan.
SO BRITISH JOURNAL OF DERMATOLOGY, **(1999 Jun)** 140 (6) 1130-2. Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE) (TWIN STUDY)
LA English
FS Priority Journals
EM 200007
EW 20000704
AB Genomic DNA extracted from peripheral blood mononuclear cells of monozygotic twin patients with urticaria pigmentosa was investigated for mutations of proto-oncogene c-kit. Neither the patients nor their families had genomic mutations in exon 11 or exon 17 of c-kit. The patients did not have any systemic involvement or bone marrow abnormalities. There are indications that some genetic factors may participate in the pathogenesis of urticaria pigmentosa in monozygotic twins. In the present patients, factors other than genomic faults in exon 11 and exon 17 of c-kit may be responsible for the pathogenesis.
CT Check Tags: Female; Human
Adult
*Diseases in Twins: GE, genetics
Exons

Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
Sequence Analysis, DNA
*Twins, Monozygotic
***Urticaria Pigmentosa: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 12 OF 109 MEDLINE
AN 1999282212 MEDLINE
DN 99282212
TI Lack of c-kit mutation in familial urticaria pigmentosa.
AU Rosbotham J L; Malik N M; Syrris P; Jeffery S; Bedlow A; Gharraie S; Murday V A; Holden C A; Carter N D
CS Department of Dermatology, St Helier Hospital, Carshalton, Surrey SM5 1AA, U.K.
SO BRITISH JOURNAL OF DERMATOLOGY, **(1999 May)** 140 (5) 849-52.
Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200007
EW 20000701
AB Somatic mutations within c-kit have been reported in individuals with mastocytoses, including urticaria pigmentosa (UP). We have identified three siblings with UP. We aimed to determine whether the c-kit proto-oncogene was playing a part in the aetiology of UP in these three siblings. Using seven microsatellite repeat markers spanning an 8-cM interval encompassing the c-kit gene we followed the transmission of the c-kit gene in this family. Furthermore, single-strand conformation polymorphism analysis was used to scan exon 17 of the c-kit gene for mutations in genomic DNA of all family members and somatic DNA extracted from skin of the eldest affected sibling, the proband. No mutations were found in exon 17 in either genomic DNA of all family members or somatic DNA of the proband. Patients with UP have been shown to possess somatic mutations of the c-kit gene. However, this locus has been excluded as playing a part in the three siblings examined here in whom a second gene locus must be determining their UP. Therefore, this study emphasizes genetic heterogeneity in UP. Future study to identify primary molecular determinants of UP should include affected sib-pair studies.
CT Check Tags: Case Report; Female; Human; Male; Support, Non-U.S. Gov't
Child, Preschool
Chromosome Mapping
DNA Mutational Analysis
Exons
Haplotypes
Heterozygote
Pedigree
Polymorphism, Single-Stranded Conformational
***Proto-Oncogene Protein c-kit: GE, genetics**
***Urticaria Pigmentosa: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 13 OF 109 MEDLINE
AN 1999272178 MEDLINE
DN 99272178
TI Increased cutaneous immunoreactive stem cell factor expression and serum stem cell factor level in systemic scleroderma.
AU Kihira C; Mizutani H; Asahi K; Hamanaka H; Shimizu M
CS Department of Dermatology, Mie University, Faculty of Medicine, Japan.
SO JOURNAL OF DERMATOLOGICAL SCIENCE, **(1998 May)** 20 (1) 72-8.
Journal code: AY9. ISSN: 0923-1811.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199909
EW 19990902
AB Skin **hyperpigmentation** and itching are characteristic findings in systemic sclerosis (SSC) patients. Stem cell factor (SCF, c-kit ligand) is a multifunctional cytokine which can promote melanocyte and mast cell development. We investigated the SCF expression histopathologically in normal and SSC skin, and compared the expression with the serum SCF levels measured with a specific enzyme-linked immunosorbent assay. The epidermal and dermal immunoreactive SCF expression was markedly higher in the forearm skin of edematous phase SSC patients than in that of normal subjects. Tissue SCF expression declined from the sclerotic phase to the atrophic phase, where it was close to the normal level. In contrast, the elevated serum SCF level seen in the edematous phase samples was further increased in the sclerotic phase samples. The serum SCF level decreased in the atrophic phase, but it still remained at a level higher than that of the normal controls. Itching and increase of dermal mast cell number are characteristic of edematous phase SSC, and are in bears a parallel to the presently observed dermal SCF expression profile. Pigmentation is significant in sclerotic phase SSC and lasts to the atrophic phase, which may correspond to the serum SCF level observed here. These results indicate a contribution of the fibroblast membrane integral SCF in dermal mast cell development, and of the soluble serum SCF to melanocyte activation in SSC.
CT Check Tags: Female; Human; Support, Non-U.S. Gov't
Adult
Aged
Blotting, Western
Enzyme-Linked Immunosorbent Assay
Immunohistochemistry
Middle Age
Reference Values
Scleroderma, Systemic: BL, blood
Scleroderma, Systemic: IM, immunology
***Scleroderma, Systemic: ME, metabolism**
Skin: IM, immunology
***Skin: ME, metabolism**
***Stem Cell Factor: BI, biosynthesis**
***Stem Cell Factor: BL, blood**
Stem Cell Factor: IM, immunology
CN **0 (Stem Cell Factor)**

L42 ANSWER 14 OF 109 MEDLINE
AN 1999250412 MEDLINE
DN 99250412
TI Removal of stem cell factor or addition of monoclonal anti-c-KIT antibody induces apoptosis in murine melanocyte precursors.
AU Ito M; Kawa Y; Ono H; Okura M; Baba T; Kubota Y; Nishikawa S I; Mizoguchi M
CS Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1999 May)** 112 (5) 796-801.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199908
AB Previous findings indicate that the protein c-KIT and its ligand, stem cell factor (SCF) play a crucial role in the development of melanocytes from their precursors in the embryonic neural crest cells. Using a monoclonal anti-c-KIT antibody, ACK2, which is an antagonistic blocker of c-KIT function, we and colleagues demonstrated that mouse melanocytes disappeared with the injection of ACK2 during certain periods of embryonic and postnatal life. The precise mechanisms of this disappearance, however, remain unclear. Because melanocytes disappeared without any inflammation

in these in vivo studies, we suspect that apoptosis was a main cause of their disappearance. In this study, to clarify the underlying mechanism, we studied whether ACK2 induces apoptosis in c-KIT-positive melanoblasts, which appear in mouse neural crest cells cultured with SCF from 9.5 d old mouse embryos. With an in situ apoptosis detection kit, a significant increase in apoptosis was detected after the removal of SCF, which further increased with the addition of ACK2 during SCF-dependent periods. The occurrence of apoptosis in the cultured cells was also demonstrated by a DNA analysis and electron microscopy. Immunohistochemical double staining confirmed that the apoptotic cells were c-KIT positive, and the electron microscopy showed that these apoptotic cells were melanocyte precursors. It was therefore demonstrated that apoptosis was induced in the SCF-dependent c-KIT-positive melanocytes in vitro when the SCF/c-KIT interaction was obstructed. These findings elucidate the mechanism of the regulation of melanocyte development, and the survival and proliferation of these precursor cells, by SCF/c-KIT interaction.

CT Check Tags: Animal
*Antibodies, Monoclonal: PD, pharmacology
*Apoptosis
Binding, Competitive
Cells, Cultured
Dose-Response Relationship, Drug
DNA Fragmentation: DE, drug effects
Embryo
Immunohistochemistry
***Melanocytes: CY, cytology**
Melanocytes: DE, drug effects
Melanocytes: ME, metabolism
Melanocytes: UL, ultrastructure
Mice
Mice, Inbred C57BL
Microscopy, Electron
*Neural Crest: CY, cytology
Neural Crest: DE, drug effects
Neural Crest: ME, metabolism
Neural Crest: UL, ultrastructure
Proto-Oncogene Protein c-kit: IM, immunology
Proto-Oncogene Protein c-kit: ME, metabolism
***Proto-Oncogene Protein c-kit: PH, physiology**
Stem Cell Factor: PD, pharmacology
***Stem Cell Factor: PH, physiology**
***Stem Cells: CY, cytology**
Stem Cells: DE, drug effects
Stem Cells: ME, metabolism
Stem Cells: UL, ultrastructure

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Antibodies, Monoclonal); **0 (Stem Cell Factor)**

L42 ANSWER 15 OF 109 MEDLINE
AN 1999250079 MEDLINE
DN 99250079
TI Increased serum level of stem cell factor in association with disease progression of **hyperpigmented** mycosis fungoides [letter] [published erratum appears in Br J Dermatol 1999 Nov;141(5):100].
AU Yamamoto T; Katayama I; Nishioka K
SO BRITISH JOURNAL OF DERMATOLOGY, **(1999 Apr)** 140 (4) 765-6. Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Letter
LA English
FS Priority Journals
EM 200006
CT Check Tags: Case Report; Human; Male
Hyperpigmentation: BL, blood
Hyperpigmentation: PA, pathology
Middle Age

*Mycosis Fungoides: BL, blood
Mycosis Fungoides: PA, pathology
***Skin Neoplasms: BL, blood**
Skin Neoplasms: PA, pathology
***Stem Cell Factor: BL, blood**
CN **0 (Stem Cell Factor)**

L42 ANSWER 16 OF 109 MEDLINE
AN 1999208021 MEDLINE
DN 99208021
TI Hepatocyte growth factor/scatter factor-MET signaling in neural crest-derived melanocyte development.
AU Kos L; Aronzon A; Takayama H; Maina F; Ponzetto C; Merlino G; Pavan W
CS Laboratory for Genetic Disease Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-4472, USA.
SO PIGMENT CELL RESEARCH, **(1999 Feb)** 12 (1) 13-21.
Journal code: PIG. ISSN: 0893-5785.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
AB The mechanisms governing development of neural crest-derived melanocytes, and how alterations in these pathways lead to hypopigmentation disorders, are not completely understood. Hepatocyte growth factor/scatter factor (HGF/SF) signaling through the tyrosine-kinase receptor, MET, is capable of promoting the proliferation, increasing the motility, and maintaining high tyrosinase activity and melanin synthesis of melanocytes in vitro. In addition, transgenic mice that ubiquitously overexpress HGF/SF demonstrate **hyperpigmentation** in the skin and leptomenigenes and develop melanomas. To investigate whether HGF/ SF-MET signaling is involved in the development of neural crest-derived melanocytes, transgenic embryos, ubiquitously overexpressing HGF/SF, were analyzed. In HGF/SF transgenic embryos, the distribution of melanoblasts along the characteristic migratory pathway was not affected. However, additional ectopically localized melanoblasts were also observed in the dorsal root ganglia and neural tube, as early as 11.5 days post coitus (p.c.). We utilized an in vitro neural crest culture assay to further explore the role of HGF/SF-MET signaling in neural crest development. HGF/SF added to neural crest cultures increased melanoblast number, permitted differentiation into pigmented melanocytes, promoted melanoblast survival, and could replace mast-cell growth factor/Steel factor (MGF) in explant cultures. To examine whether HGF/SF-MET signaling is required for the proper development of melanocytes, embryos with a targeted Met null mutation (Met-/-) were analysed. In Met-/- embryos, melanoblast number and location were not overtly affected up to 14 days p.c. These results demonstrate that HGF/SF-MET signaling influences, but is not required for, the initial development of neural crest-derived melanocytes in vivo and in vitro.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Differentiation: DE, drug effects
Cell Division
Cells, Cultured
Embryo: DE, drug effects
Gestational Age
Hepatocyte Growth Factor: GE, genetics
*Hepatocyte Growth Factor: ME, metabolism
Hepatocyte Growth Factor: PD, pharmacology
Melanocytes: DE, drug effects
***Melanocytes: PH, physiology**
Mice
Mice, Transgenic
*Neural Crest: CY, cytology
*Neural Crest: EM, embryology
Neural Crest: ME, metabolism
***Proto-Oncogene Protein c-met: ME, metabolism**

***Signal Transduction: PH, physiology**
Stem Cell Factor: ME, metabolism
Stem Cell Factor: PD, pharmacology
RN 67256-21-7 (Hepatocyte Growth Factor)
CN EC 2.7.11.- (Proto-Oncogene Protein c-met); **0 (Stem Cell Factor)**

L42 ANSWER 17 OF 109 MEDLINE
AN 1999092927 MEDLINE
DN 99092927
TI Development of melanocyte progenitors in murine Steel mutant neural crest explants cultured with stem cell factor, endothelin-3, or TPA.
AU Ono H; Kawa Y; Asano M; Ito M; Takano A; Kubota Y; Matsumoto J; Mizoguchi M
CS Department of Biology, Keio University, Yokohama, Japan.. ono@hc.keio.ac.jp
SO PIGMENT CELL RESEARCH, **(1998 Oct)** 11 (5) 291-8.
Journal code: PIG. ISSN: 0893-5785.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
AB Stem cell factor (SCF) has been suggested to be indispensable for the development of neural crest cells into melanocytes because Steel mutant mice (i.e., Sl/Sl(d)) have no pigmented hairs. On the other hand, it has been demonstrated that the addition of endothelin 3 (ET-3) or TPA to neural crest cell cultures can induce melanocyte differentiation without addition of extrinsic SCF. In this study, we excluded the influence of intrinsic SCF by using Sl/Sl mouse embryos to study more precisely the effects of natural cytokines, such as extrinsic soluble SCF or ET-3, or chemical reagents, such as TPA or cholera toxin. We found that SCF is supplied within the wild-type neural crest explants and that ET-3 cannot induce melanocyte differentiation or proliferation without SCF. These results indicate that SCF plays a critical role in survival or G1/S entry of melanocyte progenitors and that SCF initially stimulates their proliferation and then ET-3 accelerates their proliferation and differentiation. TPA has the ability to elicit neural crest cell differentiation into melanocytes without exogenously added SCF but it is not as effective as SCF because many more melanocytes developed in the wild-type neural crest explants cultured with TPA.
CT Check Tags: Animal; In Vitro
Cholera Toxin: ME, metabolism
Dopa: ME, metabolism
*Endothelin-3: PD, pharmacology
Genotype
Immunohistochemistry
***Melanocytes: PH, physiology**
Mice
Muridae: GE, genetics
Mutation
*Neural Crest: CY, cytology
Proto-Oncogene Protein c-kit: ME, metabolism
***Stem Cell Factor: GE, genetics**
Stem Cell Factor: ME, metabolism
***Stem Cell Factor: PD, pharmacology**
***Stem Cells: PH, physiology**
*Tetradecanoylphorbol Acetate: PD, pharmacology
Tissue Culture
Tissue Distribution
RN 16561-29-8 (Tetradecanoylphorbol Acetate); 63-84-3 (Dopa); 9012-63-9 (Cholera Toxin)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Endothelin-3); **0 (Stem Cell Factor)**

L42 ANSWER 18 OF 109 MEDLINE
AN 1999073936 MEDLINE

DN 99073936
TI Systemic mastocytosis associated with acute myeloid leukaemia: report of two cases and detection of the c-kit mutation Asp-816 to Val.
AU Sperr W R; Walchshofer S; Horny H P; Fodinger M; Simonitsch I; Fritsche-Polanz R; Schwarzinger I; Tschachler E; Sillaber C; Hagen W; Geissler K; Chott A; Lechner K; Valent P
CS Department of Internal Medicine I, University of Vienna, Austria.
SO BRITISH JOURNAL OF HAEMATOLOGY, **(1998 Dec)** 103 (3) 740-9.
Journal code: AXC. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199903
AB A subset of patients with systemic mastocytosis (SM) develop acute myeloid leukaemia (AML). However, little is known about the biology of such leukaemias and their relationship to the mast cell (MC) lineage. We report on two female patients who suffered from SM and AML. According to FAB criteria, the leukaemias were classified as AML-M4 (patient 1) and AML-MO (patient 2). The coexistence of the two distinct neoplasms (AML and SM) was demonstrable by immunostaining of serial bone marrow (BM) sections with monoclonal antibodies (mAb). In particular, the MC infiltrates were found to react with mAb against MC-tryptase and MC growth factor receptor c-kit (CD117), but not with mAb to CD15 or CD34. In contrast, the AML blasts were immunoreactive for CD15 (patient 1) or CD34 (patient 2), but did not express tryptase. The c-kit point mutation Asp-->Val at codon 816, considered to play a role in the transformation of MC progenitors, was detected in patient 1 in a BM cell fraction containing 4% MC. However, no c-kit mutation was found in pure AML blasts (<1% MC). These findings argue against an evolution of the AML clone from neoplastic MC or MC-committed progenitors.
CT Check Tags: Case Report; Female; Human; Support, Non-U.S. Gov't
Acute Disease
Aged
Antigens, CD: ME, metabolism
Immunohistochemistry
Leukemia, Myeloid: CO, complications
*Leukemia, Myeloid: GE, genetics
Leukemia, Myeloid: ME, metabolism
Mastocytosis: CO, complications
***Mastocytosis: GE, genetics**
Mastocytosis: ME, metabolism
Middle Age
*Point Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
Proto-Oncogene Protein c-kit: ME, metabolism
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Antigens, CD)

L42 ANSWER 19 OF 109 MEDLINE
AN 1999072667 MEDLINE
DN 99072667
TI Identification of activating c-kit mutations in adult-, but not in childhood-onset indolent mastocytosis: a possible explanation for divergent clinical behavior.
AU Buttner C; Henz B M; Welker P; Sepp N T; Grabbe J
CS Department of Dermatology, Charite, Humboldt University, Berlin, Germany.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1998 Dec)** 111 (6) 1227-31.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199903
AB Mastocytosis represents a mast cell proliferative disease that generally runs a benign clinical course, with spontaneous remissions mostly by

puberty in childhood-onset disease, although rare forms, particularly in adult-onset disease, can be associated with (pre)malignant hematologic disorders and very rarely present as mast cell leukemia or malignant mastocytosis. Reasons for this divergent clinical behavior of childhood- versus adult-onset disease are unknown. Recently, two activating mutations in the intracellular domain of the proto-oncogene c-kit, which encodes a tyrosine kinase receptor for the mast cell growth factor stem cell factor, have been detected in the human leukemic mast cell line HMC-1. We have therefore studied lesional skin biopsies from patients with adult- and childhood-onset indolent mastocytosis for the presence of these codon 560 and 816 mutations. C-kit coding DNA sequences were amplified and analyzed by mutation-specific restriction analyses, and mutated polymerase chain reaction products were additionally cloned and sequenced. The codon 816 mutation was found in all six samples from adult patients, but not in any of the 11 specimens from children. In addition, the codon 560 mutation could be demonstrated for the first time in indolent mastocytosis, namely in two of four specimens from adult patients, but not in those from two children. These data thus provide a possible explanation for the divergent clinical behavior of adult- versus childhood-onset indolent mastocytosis, with the first being associated with an activating mutation, possibly as part of a neoplastic process, and the latter representing most likely a reactive process of an as yet unknown pathogenesis.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
*Age of Onset
Biopsy
Cell Count
Child
Child, Preschool
Cloning, Molecular
Dyes
Genes, Structural
Infant
Mast Cells: CY, cytology
***Mastocytosis: EP, epidemiology**
***Mastocytosis: GE, genetics**
Middle Age
***Proto-Oncogene Protein c-kit: GE, genetics**
Skin: PA, pathology
Tolonium Chloride
Tumor Cells, Cultured

RN 92-31-9 (Tolonium Chloride)

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Dyes)

L42 ANSWER 20 OF 109 MEDLINE

AN 1999045317 MEDLINE

DN 99045317

TI Multilineage involvement and erythropoietin-"independent" erythroid progenitor cells in a patient with systemic mastocytosis.

AU Afonja O; Amorosi E; Ashman L; Takeshita K

CS Department of Medicine, Kaplan Comprehensive Cancer Center, New York University Medical Center, NY 10016, USA.

NC T32HL07151 (NHLBI)

SO ANNALS OF HEMATOLOGY, **(1998 Oct)** 77 (4) 183-6.
Journal code: A2P. ISSN: 0939-5555.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199902

AB We report on a patient with systemic mastocytosis with an activating point mutation of the c-kit gene. This mutation was identical to the c-kit mutation recently described by other groups. Additionally, we found that in this patient the mutation was also present in myeloid and erythroid lineages, indicating a multilineage involvement and suggesting a clonal origin of the disease similar to that described in other

myeloproliferative disorders. The erythroid involvement was further demonstrated by the presence of erythropoietin-"independent" erythroid progenitor cells.
CT Check Tags: Case Report; Human; Male; Support, U.S. Gov't, P.H.S.
Cell Lineage
***Erythroid Progenitor Cells: PH, physiology**
*Erythropoietin: PH, physiology
Mastocytosis: BL, blood
***Mastocytosis: GE, genetics**
Middle Age
Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
RN 11096-26-7 (Erythropoietin)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 21 OF 109 MEDLINE
AN 1999043418 MEDLINE
DN 99043418
TI Clinical correlates of the presence of the Asp816Val c-kit mutation in the peripheral blood mononuclear cells of patients with mastocytosis.
AU Worobec A S; Semere T; Nagata H; Metcalfe D D
CS Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-1881, USA.
SO CANCER, **(1998 Nov 15)** 83 (10) 2120-9.
Journal code: CLZ. ISSN: 0008-543X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199902
AB BACKGROUND: The Asp816Val mutation in the catalytic domain of the c-kit receptor has been identified in patients with systemic mastocytosis. METHODS: To determine whether this mutation is associated with identifiable clinical patterns of disease and prognosis, a total of 65 patients with mastocytosis were screened for the presence of the Asp816Val mutation in peripheral blood mononuclear cells (PBMCs). RESULTS: By analysis of HinfI digestion products, the authors found that the overall prevalence of this mutation in the current patient series was 25%. The presence of the Asp816Val mutation in PBMCs was observed in 15 adults (of 16 Asp816Val mutation positive patients) and 1 infant, but not in any children with mastocytosis. Patients whose PBMCs were positive for this mutation (category II and a subset of category Ib mastocytosis patients) manifested a more severe disease pattern, with clinical features ranging in severity from early to advanced myelodysplastic or myeloproliferative syndromes. These patients more commonly had osteosclerotic bone involvement (a clinical feature primarily observed in mastocytosis patients with an associated hematologic disorder) as well as immunoglobulin dysregulation and peripheral blood abnormalities. Furthermore, pedigree analysis of three families provided evidence that the mutation was somatic. CONCLUSIONS: Twenty-five percent of all patients with mastocytosis had the Asp816Val mutation in PBMCs; 56% of these patients had evidence of a myelodysplastic or myeloproliferative syndrome, and 44% had been clinically placed in the indolent mastocytosis category, suggesting that the current classification scheme used to assign prognosis may be inadequate. Therefore, determination of the presence or absence of this mutation in PBMCs of mastocytosis patients offers a useful adjunct in determining the extent of workup and assigning prognosis in this complex and heterogeneous disease.
CT Check Tags: Female; Human; Male
Adolescence
Adult
Age Factors
Aged
Aged, 80 and over
Bone Diseases: RA, radiography

Child
Child, Preschool
Infant
*Leukocytes, Mononuclear: CH, chemistry
Mastocytosis: BL, blood
***Mastocytosis: GE, genetics**
Mastocytosis: PA, pathology
Middle Age
*Point Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 22 OF 109 MEDLINE
AN 1999038199 MEDLINE
DN 99038199
TI Targeting the microphthalmia basic helix-loop-helix-leucine zipper transcription factor to a subset of E-box elements in vitro and in vivo.
AU Aksan I; Goding C R
CS Eukaryotic Transcription Laboratory, Marie Curie Research Institute, The Chart, Oxted, Surrey RH8 0TL, United Kingdom.
SO MOLECULAR AND CELLULAR BIOLOGY, **(1998 Dec)** 18 (12) 6930-8.
Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
AB The development of melanocytes, which are pigment-producing cells responsible for skin, hair, and eye color, is absolutely dependent on the action of the microphthalmia basic helix-loop-helix-leucine zipper (bHLH-LZ) transcription factor (Mi); mice lacking a functional Mi protein are entirely devoid of pigment cells. Mi has been shown to activate transcription of the tyrosinase, TRP-1, TRP-2, and QNR-71 genes through specific E-box elements, most notably the highly conserved M box. We investigated the mechanism which enables Mi to be recruited specifically to a restricted subset of E boxes in target promoters while being prevented from binding E-box elements in other promoters. We show both in vitro and in vivo that the presence of a T residue flanking a CATGTG E box is an essential determinant of the ability of Mi to bind DNA, and we successfully predict that the CATGTG E box from the P gene would not bind Mi. In contrast, no specific requirement for the sequences flanking a CACGTG E box was observed, and no binding to an atypical E box in the c-Kit promoter was detected. The relevance of these observations to the control of melanocyte-specific gene expression was highlighted by the fact that the E-box elements located in the tyrosinase, TRP-1, TRP-2, and QNR-71 promoters without exception possess a 5' flanking T residue which is entirely conserved between species as diverse as man and turtle. The ability of Mi to discriminate between different E-box motifs provides a mechanism to restrict the repertoire of genes which are likely to be regulated by Mi and provides insight into the ability of bHLH-LZ transcription factors to achieve the specificity required for the precise coordination of transcription during development.
CT Check Tags: Human; Support, Non-U.S. Gov't
Conserved Sequence: GE, genetics
Dimerization
DNA-Binding Proteins: GE, genetics
*DNA-Binding Proteins: ME, metabolism
Genes, Regulator: GE, genetics
Genes, Reporter: GE, genetics
*Helix-Loop-Helix Motifs: GE, genetics
*Leucine Zippers: GE, genetics
***Melanocytes: ME, metabolism**
Monophenol Monooxygenase: GE, genetics
Promoter Regions (Genetics): GE, genetics
Proto-Oncogene Protein c-kit: GE, genetics
*Transcription Factors: GE, genetics

CN EC 1.14.18.1 (Monophenol Monooxygenase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (transcription factor USF); 0 (DNA-Binding Proteins); 0 (Mi protein); 0 (Transcription Factors)

L42 ANSWER 23 OF 109 MEDLINE
AN 1998439533 MEDLINE
DN 98439533
TI Cytogenetic abnormalities and their lack of relationship to the Asp816Val c-kit mutation in the pathogenesis of mastocytosis.
AU Worobec A S; Akin C; Scott L M; Metcalfe D D
CS Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-1881, USA.
SO JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, **(1998 Sep)** 102 (3) 523-4.
Journal code: H53. ISSN: 0091-6749.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199901
CT Check Tags: Human
Asparagine: GE, genetics
*Chromosome Aberrations
Leukocytes, Mononuclear: PH, physiology
Mastocytosis: BL, blood
***Mastocytosis: GE, genetics**
*Point Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
Reverse Transcriptase Polymerase Chain Reaction
Valine: GE, genetics
RN 7004-03-7 (Valine); 7006-34-0 (Asparagine)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 24 OF 109 MEDLINE
AN 1998435884 MEDLINE
DN 98435884
TI Phenotypic characterization of human skin mast cells by combined staining with toluidine blue and CD antibodies.
AU Ghannadan M; Baghestanian M; Wimazal F; Eisenmenger M; Latal D; Kargul G; Walchshofer S; Sillaber C; Lechner K; Valent P
CS Department of Internal Medicine I, University of Vienna, Austria.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1998 Oct)** 111 (4) 689-95.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199901
AB Mast cells (MC) are important cellular components of the immune network in diverse organs. The skin MC has likewise been implicated in IgE- and complement-mediated cutaneous reactions. Such reactions supposedly involve specific cell surface membrane receptors. In this study, the cell surface marker profile of human skin MC was established using monoclonal antibodies (MoAb) against defined CD antigens. MC were isolated from juvenile foreskin (n = 55) and adult mammary skin (n = 5). The reactivity of MC with MoAb was assessed by a combined toluidine blue/immunofluorescence staining technique. Confirming our previous analyses on lung MC, foreskin MC reacted with MoAb against CD9, CD29, CD33, CD43, CD44, CD45, CD46, CD51, CD54, CD55, CD58, CD59, CD61, and CD117 (c-kit). Foreskin MC were also recognized by MoAb to CD47, CD48, CD49d, CD53, CD60, CD63, CD81, CD82, CD84, CD87, CD92, CD97, CD98, and CD99. Recently clustered CD antigens detectable on foreskin MC were CD147 (neurothelin), CD149 (MEM133), CD151 (PETA-3), and CD157 (BST-1). In contrast to lung MC and MC from adult skin, foreskin MC were found to express CD88 (C5aR). Also, cutaneous MC (from both juvenile foreskin and

adult mammary skin), but not lung MC, were found to bind the CD32 MoAb IV.3, 2E1, and FLI8.26 (Fc gammaRII). The CD50 antigen (ICAM-3) was detectable on lung MC, but not on foreskin MC or MC of adult mammary skin. In summary, our data show that cutaneous MC and lung MC express an almost identical phenotype; however, in contrast to lung MC, cutaneous MC appear to express substantial amounts of CD32 and to lack CD50. In addition, foreskin MC, unlike MC from adult skin or lung, express CD88.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adolescence
Adult
Antibodies
Antigens, CD: IM, immunology
Antigens, CD29: BI, biosynthesis
Cells, Cultured
Child
Child, Preschool
Dyes
Immunophenotyping
Infant
Mast Cells: CY, cytology
*Mast Cells: ME, metabolism
Phenotype
Proto-Oncogene Protein c-kit: BI, biosynthesis
Receptors, Complement: ME, metabolism
Receptors, IgE: BI, biosynthesis
Receptors, IgG: BI, biosynthesis
Receptors, Virus: ME, metabolism
Skin: CH, chemistry
***Skin: CY, cytology**
Stem Cell Factor
Tolonium Chloride

RN 92-31-9 (Tolonium Chloride)

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Antibodies); 0 (Antigens, CD); 0 (Antigens, CD29); 0 (Dyes); 0 (Receptors, Complement); 0 (Receptors, IgE); 0 (Receptors, IgG); 0 (Receptors, Virus); **0 (Stem Cell Factor)**

L42 ANSWER 25 OF 109 MEDLINE
AN 1998363320 MEDLINE
DN 98363320
TI A novel KIT gene missense mutation in a Japanese family with piebaldism [letter].
AU Nomura K; Hatayama I; Narita T; Kaneko T; Shiraishi M
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1998 Aug)** 111 (2) 337-8. Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Letter
LA English
FS Priority Journals; Cancer Journals
EM 199810
CT Check Tags: Female; Human
Amino Acid Sequence
Child, Preschool
Molecular Sequence Data
Mutation
***Piebaldism: GE, genetics**
Proto-Oncogene Protein c-kit: CH, chemistry
***Proto-Oncogene Protein c-kit: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 26 OF 109 MEDLINE
AN 1998363303 MEDLINE
DN 98363303
TI The SCF/KIT pathway plays a critical role in the control of normal human melanocyte homeostasis [see comments].
CM Comment in: J Invest Dermatol 1999 Jul;113(1):139-40

AU Grichnik J M; Burch J A; Burchette J; Shea C R
CS Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1998 Aug)** 111 (2) 233-8.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199810
AB During development, the interaction of stem cell factor (SCF) with its receptor, KIT, is critical for the survival of melanocytes. Limited in vivo human studies have suggested a possible activating role of SCF on adult human melanocytes. In order to study the impact of this pathway on normal melanocyte homeostasis, human skin xenografts were treated with serial injections of recombinant human SCF or a KIT-inhibitory antibody (K44.2). On histologic evaluation, SCF injection increased, whereas KIT inhibition decreased the number, size, and dendricity of melanocytes. Immunohistochemical expression of melanocyte differentiation antigens, including tyrosinase-related-protein-1 and gp100/pmel17, was markedly increased by treatment with SCF, and decreased by K44.2 treatment. The number of Ki67-positive melanocytes was increased in the SCF-treated tissue, suggesting a direct proliferative effect of SCF; conversely, treatment with K44.2 resulted in melanocyte loss, which did not appear reversible with prolonged treatment. These findings demonstrate that the SCF/KIT pathway remains critical in adult human skin, and that pharmacologic modulation of this single pathway can control cutaneous melanocyte homeostasis.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Cell Count
*Homeostasis
Interferon Type I: AN, analysis
Ki-67 Antigen: AN, analysis
***Melanocytes: DE, drug effects**
Melanocytes: PH, physiology
Mice
Proteins: AN, analysis
***Proto-Oncogene Protein c-kit: PH, physiology**
Skin Transplantation
***Stem Cell Factor: PD, pharmacology**
Transplantation, Heterologous
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (tyrosinase-related protein); 0 (Interferon Type I); 0 (Ki-67 Antigen); 0 (Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 27 OF 109 MEDLINE
AN 1998337165 MEDLINE
DN 98337165
TI Congenital bullous mastocytosis with myeloproliferative disorder and c-kit mutation.
AU Shah P Y; Sharma V; Worobec A S; Metcalfe D D; Zwick D C
CS Department of Pediatrics, University of Illinois at Chicago, USA.
SO JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, **(1998 Jul)** 39 (1) 119-21.
Journal code: HVG. ISSN: 0190-9622.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199810
CT Check Tags: Case Report; Human; Male
Aspartic Acid: GE, genetics
Bone Marrow: PA, pathology
Fatal Outcome
Granulocytes: PA, pathology
Hyperplasia

Infant, Newborn
Leukocytosis: PA, pathology
Mast Cells: PA, pathology
*Myeloproliferative Disorders: CN, congenital
*Point Mutation: GE, genetics
***Proto-Oncogene Protein c-kit: GE, genetics**
***Urticaria Pigmentosa: CN, congenital**
Urticaria Pigmentosa: GE, genetics
Valine: GE, genetics
RN 56-84-8 (Aspartic Acid); 7004-03-7 (Valine)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 28 OF 109 MEDLINE
AN 1998324991 MEDLINE
DN 98324991
TI Lineage-specific signaling in melanocytes. C-kit stimulation recruits p300/CBP to microphthalmia.
AU Price E R; Ding H F; Badalian T; Bhattacharya S; Takemoto C; Yao T P; Hemesath T J; Fisher D E
CS Pediatric Hematology/Oncology, Dana Farber Cancer Research Institute and Harvard Medical School, Boston, Massachusetts 02115, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1998 Jul 17)** 273 (29) 17983-6.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
AB During melanocyte development, the cytokine Steel factor activates its receptor c-Kit, initiating a signal transduction cascade, which is vital for lineage determination via unknown downstream nuclear targets. c-Kit has recently been found to trigger mitogen-activated protein kinase-mediated phosphorylation of Microphthalmia (Mi), a lineage-restricted transcription factor, which, like Steel factor and c-Kit, is essential for melanocyte development. This cascade results in increased Mi-dependent transcriptional reporter activity. Here we examine the mechanism by which Mi is activated by this pathway. Phosphorylation does not significantly alter Mi's nuclear localization, DNA binding, or dimerization. However, the transcriptional coactivator p300/CBP selectively associates with mitogen-activated protein kinase-phosphorylated Mi, even under conditions in which non-MAPK phospho-Mi is more abundant. Moreover, p300/CBP coactivates Mi transcriptional activity in a manner dependent upon this phosphorylation. Mi thus joins CREB as a transcription factor whose signal-responsive phosphorylation regulates coactivator recruitment, in this case modulating lineage development in melanocytes.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Dimerization
DNA-Binding Proteins: GE, genetics
*DNA-Binding Proteins: PH, physiology
Enzyme Activation
Hamsters
***Melanocytes: PH, physiology**
Mice
*Nuclear Proteins: PH, physiology
Phosphorylation
Protein Binding
Proto-Oncogene Protein c-kit: PH, physiology
Rabbits
***Signal Transduction**
Stem Cell Factor: PH, physiology
Trans-Activation (Genetics)
*Trans-Activators: PH, physiology
*Transcription Factors: PH, physiology

Tumor Cells, Cultured
CN EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (CREB-binding protein); 0 (DNA-Binding Proteins); 0 (E1A-associated p300 protein); 0 (Mi protein); 0 (Nuclear Proteins); **0 (Stem Cell Factor)**; 0 (Trans-Activators); 0 (Transcription Factors)

L42 ANSWER 29 OF 109 MEDLINE
AN 1998322243 MEDLINE
DN 98322243
TI Transgene expression of steel factor in the basal layer of epidermis promotes survival, proliferation, differentiation and migration of melanocyte precursors.
AU Kunisada T; Yoshida H; Yamazaki H; Miyamoto A; Hemmi H; Nishimura E; Shultz L D; Nishikawa S; Hayashi S
CS Department of Immunology, School of Life Science, Faculty of Medicine, Tottori University, Nishi-machi 86, Yonago 683, Japan.. tkunisad@grape.med.tottori-u.ac.jp
SO DEVELOPMENT, **(1998 Aug)** 125 (15) 2915-23.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
AB Mutations at the murine dominant white spotting (KitW) and steel (MgfSl) loci, encoding c-Kit receptor kinase and its ligand respectively, exert developmental defects on hematopoietic cells, melanocytes, germ cells and interstitial cells of Cajal. The expression patterns of steel factor (SLF) observed in the skin and gonads suggest that SLF mediates a migratory or a chemotactic signal for c-Kit-expressing stem cells (melanocyte precursors and primordial germ cells). By targeting expression of SLF to epidermal keratinocytes in mice, we observed extended distribution of melanocytes in a number of sites including oral epithelium and footpads where neither melanocytes nor their precursors are normally detected. In addition, enlarged pigmented spots of KitW and other spotting mutant mice were observed in the presence of the SLF transgene. These results provide direct evidence that SLF stimulates migration of melanocytes in vivo. We also present data suggesting that SLF does not simply support survival and proliferation of melanocytes but also promotes differentiation of these cells. Unexpectedly, melanocyte stem cells independent of the c-Kit signal were maintained in the skin of the SLF transgenic mice. After the elimination of c-Kit-dependent melanoblasts by function-blocking anti-c-Kit antibody, these stem cells continued to proliferate and differentiate into mature melanocytes. These melanoblasts are able to migrate to cover most of the epidermis after several months. The SLF transgenic mice described in this report will be useful in the study of melanocyte biology.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Differentiation
Cell Movement
Cell Survival
Epidermis: CY, cytology
Keratinocytes: CY, cytology
***Melanocytes: CY, cytology**
Mice
Mice, Transgenic
Proto-Oncogene Protein c-kit: ME, metabolism
***Skin: CY, cytology**
***Skin Pigmentation: PH, physiology**
***Stem Cell Factor: BI, biosynthesis**
Stem Cell Factor: GE, genetics
***Stem Cells: CY, cytology**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit); 0 (Stem Cell Factor)**

L42 ANSWER 30 OF 109 MEDLINE
AN 1998255713 MEDLINE
DN 98255713
TI Paraffin section detection of the c-kit gene product (CD117) in human tissues: value in the diagnosis of mast cell disorders.
AU Arber D A; Tamayo R; Weiss L M
CS Division of Pathology, City of Hope National Medical Center, Duarte, CA 91010, USA.
SO HUMAN PATHOLOGY, **(1998 May)** 29 (5) 498-504.
Journal code: GEC. ISSN: 0046-8177.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199808
AB The c-kit gene product (CD117) is known to be expressed by a variety of normal human tissue cell types, including breast epithelium, germ cells, melanocytes, immature myeloid cells, and mast cells. To further characterize the expression of this antigen, 117 normal human tissues and 576 human tumors were studied by paraffin section immunohistochemistry. Varying degrees of CD117 expression were identified in various normal cells and in 53% of all tumors studied. In most cases (42% of total), CD117 expression was weak. Expression was most common in mast cell disease (100%), testicular germ cell tumors (100%), endometrial carcinomas (100%), papillary and follicular thyroid carcinomas (100%), small cell carcinomas (91%), malignant melanomas (90%), and ovarian epithelial carcinomas (87%). Strong immunoreactivity was only identified in cases of mast cell disease (11 of 11 cases), serous ovarian carcinoma (3 of 16), malignant melanoma (2 of 40), small cell lung carcinoma (one of seven), and adenoid cystic carcinoma (one of one). Although the pattern of reactivity was primarily cytoplasmic, a membrane staining pattern was seen in a subset of cases, and strong membrane staining was identified in normal mast cells and all cases of mast cell disease. The lack of tumor specificity of weak expression of this antigen limits its diagnostic utility in most cases. However, the strong membrane reactivity for CD117 identified in mast cells may be useful in the diagnosis of mast cell disorders.
CT Check Tags: Female; Human; Male
Antibody Specificity
Breast: CY, cytology
Breast: ME, metabolism
Epithelium: ME, metabolism
Immunohistochemistry
Kidney Tubules: CY, cytology
Kidney Tubules: ME, metabolism
Mast Cells: ME, metabolism
*Mast Cells: PA, pathology
***Mastocytosis: DI, diagnosis**
Mastocytosis: ME, metabolism
*Neoplasm Proteins: DU, diagnostic use
Neoplasm Proteins: ME, metabolism
*Neoplasms: DI, diagnosis
Neoplasms: ME, metabolism
Paraffin Embedding
***Proto-Oncogene Protein c-kit: DU, diagnostic use**
Proto-Oncogene Protein c-kit: ME, metabolism
Seminiferous Tubules: CY, cytology
Seminiferous Tubules: ME, metabolism
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Neoplasm Proteins)

L42 ANSWER 31 OF 109 MEDLINE
AN 1998252862 MEDLINE
DN 98252862
TI Murine cutaneous mastocytosis and epidermal melanocytosis induced by keratinocyte expression of transgenic stem cell factor.
AU Kunisada T; Lu S Z; Yoshida H; Nishikawa S; Nishikawa S; Mizoguchi M;

Hayashi S; Tyrrell L; Williams D A; Wang X; Longley B J
CS Department of Immunology, School of Life Science, Faculty of Medicine, Tottori University, Yonago 683, Japan.
NC RO1AR3356 (NIAMS)
SP30041942 (CSAP)
SO JOURNAL OF EXPERIMENTAL MEDICINE, **(1998 May 18)** 187 (10) 1565-73.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199808
EW 19980802
AB The growth and differentiation of mast cells and melanocytes require stem cell factor (SCF), the ligand for the kit receptor tyrosine kinase. SCF may exist as a membrane-bound or soluble molecule. Abnormalities of the SCF-kit signaling pathway, with increased local concentrations of soluble SCF, have been implicated in the pathogenesis of the human disease cutaneous mastocytosis, but have not yet been shown to play a causal role. To investigate both the potential of SCF to cause mastocytosis and its role in epidermal melanocyte homeostasis, we targeted the expression of SCF to epidermal keratinocytes in mice with two different transgenes controlled by the human keratin 14 promoter. The transgenes contained cDNAs that either produced SCF, which can exist in both membrane-bound and soluble forms, or SCF, which remains essentially membrane bound. Murine epidermal keratinocyte expression of membrane-bound/ soluble SCF reproduced the phenotype of human cutaneous mastocytosis, with dermal mast cell infiltrates and epidermal **hyperpigmentation**, and caused the maintenance of a population of melanocytes in the interadnexal epidermis, an area where melanocytes and melanin are found in human skin but where they are not typically found in murine skin. Expression of membrane-bound SCF alone resulted in epidermal melanocytosis and melanin production, but did not by itself cause mastocytosis. We conclude, first, that a phenotype matching that of human mastocytosis can be produced in mice by keratinocyte overproduction of soluble SCF, suggesting a potential cause of this disease. Second, we conclude that keratinocyte expression of membrane-bound SCF results in the postnatal maintenance of epidermal melanocytes in mice. Since the resulting animals have skin that more closely approximates human skin than do normal mice, their study may be more relevant to human melanocyte biology than the study of skin of normal mice.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
DNA, Complementary: GE, genetics
Gene Expression Regulation
Gene Transfer
*Keratinocytes
Keratinocytes: PA, pathology
Keratinocytes: PH, physiology
***Mastocytosis: GE, genetics**
***Melanosis: GE, genetics**
Mice
Mice, Transgenic
Stem Cell Factor: BI, biosynthesis
***Stem Cell Factor: GE, genetics**
CN 0 (DNA, Complementary); **0 (Stem Cell Factor)**

L42 ANSWER 32 OF 109 MEDLINE
AN 1998213816 MEDLINE
DN 98213816
TI Detection of mi transcription factor (MITF) mRNA in a case of myelodysplastic syndrome and bone marrow mastocytosis [published erratum appears in Wien Klin Wochenschr 1998 Mar 27;110(6):238].
AU Wimazal F; Walchshofer S; Baghestanian M; Chott A; Sperr W R; Kopp C; Sillaber C; Semper H; Horny H P; Trondle U; Fodinger M; Schwarzinger I;

Lechner K; Valent P
CS Department of Internal Medicine I, University of Vienna, Austria.
SO WIENER KLINISCHE WOCHENSCHRIFT, **(1998 Feb 13)** 110 (3) 79-88.
Journal code: XOP. ISSN: 0043-5325.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
AB Myelodysplastic syndromes (MDS) may be accompanied by systemic mastocytosis. The mechanisms which play a role in the evolution of mastocytosis, however, are not well understood. We report on a case of refractory and anemia with ringed sideroblasts (RARS), and co-existing bone marrow mastocytosis. Compact mast cell (MC) infiltrates were detected in bone marrow sections by immunohistochemistry using an antibody to tryptase. In addition, the MC were found to express c-kit, the tyrosine kinase receptor for MGF (mast cell growth factor = stem cell factor, SCF). Activating point mutations in the kinase domain of c-kit (often found in mastocytosis) were not detectable. However, the mononuclear cells (MNC) of the bone marrow expressed mRNA specific for MITF, a transcription factor that regulates expression of c-kit and differentiation of MC. Surprisingly, the c-kit ligand SCF was found to augment expression of MITF mRNA in bone marrow MNC. Whether this augmentation represents a general response (preventing loss of growth factor receptor expression during cell maturation) common to all types of hemopoietic progenitors, or is confined to (some forms of) mastocytosis, remains unknown.
CT Check Tags: Case Report; Human; Male; Support, Non-U.S. Gov't
Aged
Anemia, Refractory: GE, genetics
Anemia, Refractory: PA, pathology
Anemia, Sideroblastic: GE, genetics
Anemia, Sideroblastic: PA, pathology
*Bone Marrow: PA, pathology
*DNA-Binding Proteins: GE, genetics
Gene Expression
Mast Cells: PA, pathology
Mastocytosis: DI, diagnosis
***Mastocytosis: GE, genetics**
Myelodysplastic Syndromes: DI, diagnosis
*Myelodysplastic Syndromes: GE, genetics
Point Mutation: GE, genetics
Proto-Oncogene Protein c-kit: GE, genetics
*RNA, Messenger: GE, genetics
Stem Cell Factor: GE, genetics
*Transcription Factors: GE, genetics
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (DNA-Binding Proteins); 0 (Mi protein); 0 (RNA, Messenger); **0 (Stem Cell Factor)**; 0 (Transcription Factors)

L42 ANSWER 33 OF 109 MEDLINE
AN 1998178594 MEDLINE
DN 98178594
TI Elevated expression of the proto-oncogene c-kit in patients with mastocytosis.
AU Nagata H; Worobec A S; Semere T; Metcalfe D D
CS Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-1881, USA.
SO LEUKEMIA, **(1998 Feb)** 12 (2) 175-81.
Journal code: LEU. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199806
AB The stem cell factor (SCF)c-kit receptor interaction plays a critical role

in the development and survival of mast cells. Several studies have also associated c-kit receptor mutations with the human diseases, mastocytosis and piebaldism. Overexpression of c-kit has been reported to be associated with myeloproliferative disorders and myelodysplastic syndromes. Using peripheral blood mononuclear cells (PBMCs) from 11 patients with indolent mastocytosis (category I), mastocytosis with an associated hematologic disorder (category II), or aggressive mastocytosis (category III); a patient with CMML unassociated with mastocytosis, and PBMCs from 13 normal subjects, we examined the level of expression of c-kit mRNA along with other c-kit isoforms to determine if overexpression of the c-kit receptor was associated with mastocytosis. Using quantitative competitive PCR, c-kit mRNA levels on average were found to be statistically elevated in the five patients with mastocytosis with an associated hematologic disorder and in the patient with aggressive mastocytosis as compared with controls, but not elevated in patients with indolent mastocytosis. The relative mRNA expression for the two c-kit isoforms was not significantly different in the mastocytosis patients compared with controls. This demonstration of the overexpression of c-kit mRNA in mastocytosis, and particularly those patients with clinical evidence of myelodysplastic syndrome, adds evidence to support the conclusion that mastocytosis, at least in some patients, is a feature of myelodysplasia; and suggests that determination of c-kit mRNA expression in PBMCs may provide an additional approach to assessing prognosis.

CT Check Tags: Female; Human; Male
Adult
Aged
Gene Expression
Isomerism
Leukocytes, Mononuclear: ME, metabolism
***Mastocytosis: ME, metabolism**
Middle Age
Polymerase Chain Reaction
***Proto-Oncogene Protein c-kit: BI, biosynthesis**
Proto-Oncogene Protein c-kit: BL, blood
RNA, Messenger: BL, blood
RNA, Messenger: ME, metabolism
Transcription, Genetic

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (RNA, Messenger)

L42 ANSWER 34 OF 109 MEDLINE
AN 1998161802 MEDLINE
DN 98161802
TI Biological characterization of human fibroblast-derived mitogenic factors for human melanocytes.
AU Imokawa G; Yada Y; Morisaki N; Kimura M
CS Biological Science Laboratories, Kao Corporation, Ichikaimachi 2606, Haga, Tochigi 321-34, Japan.
SO BIOCHEMICAL JOURNAL, **(1998 Mar 15)** 330 (Pt 3) 1235-9.
Journal code: 9YO. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199807
EW 19980704
AB To clarify the paracrine linkage between human fibroblasts and melanocytes in cutaneous pigmentation, we studied the effects of human fibroblast-derived factors on the proliferation of human melanocytes. In medium conditioned for 4 days with human fibroblast culture, factors were produced that markedly stimulated DNA synthesis of human melanocytes. The stimulatory effect was higher in medium conditioned with fibroblasts from aged skin than in medium conditioned with fibroblasts from young skin, and was interrupted by inhibitors of tyrosine kinase, such as tyrphostin, genistein and herbimycin, but not by inhibitors of protein kinases C and A, such as H-7 and phloretin. The conditioned medium was also capable of activating mitogen-activated protein kinase of human melanocytes, with old

fibroblasts being more effective than young ones. Analysis of factors released into the conditioned medium revealed that levels of hepatocyte growth factor (HGF) and stem cell factor (SCF) were increased in old-fibroblast-conditioned medium compared with young-fibroblast-conditioned medium. In contrast, levels of basic fibroblast growth factor (bFGF) were similar in both media. When the conditioned medium was treated with HGF antibody with or without SCF antibody, the increase in DNA synthesis by human melanocytes was decreased to 20% of the elevated level, whereas antibodies to bFGF had no effect. Analysis of the medium conditioned for 4 days after cytokine application demonstrated that, of the cytokines tested, interleukin 1alpha and tumour necrosis factor alpha are highly effective in stimulating HGF secretion by old fibroblasts. HGF and SCF, but not bFGF, were markedly increased in culture medium in the presence of IL-1alpha, and this stimulatory effect was confined to young human fibroblasts. These findings suggest that SCF and HGF derived from human fibroblasts may play a part in regulating cutaneous pigmentation during inflammation and aging.

CT Check Tags: Human
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Cell Aging
*Cell Division: PH, physiology
Cells, Cultured
Culture Media, Conditioned
Culture Media, Serum-Free
*Cytokines: BI, biosynthesis
Cytokines: IP, isolation & purification
DNA: BI, biosynthesis
Enzyme Inhibitors: PD, pharmacology
Fibroblast Growth Factor, Basic: PD, pharmacology
Fibroblasts: CY, cytology
Fibroblasts: PH, physiology
Genistein: PD, pharmacology
*Growth Substances: BI, biosynthesis
*Hepatocyte Growth Factor: BI, biosynthesis
Interleukin-1: PD, pharmacology
Kinetics
***Melanocytes: CY, cytology**
***Melanocytes: DE, drug effects**
Phloretin: PD, pharmacology
Protein-Tyrosine Kinase: ME, metabolism
Quinones: PD, pharmacology
***Skin: CY, cytology**
Stem Cell Factor: BI, biosynthesis
Thymidine: ME, metabolism
1-(5-Isoquinolinesulfonyl)-2-methylpiperazine: PD, pharmacology

RN 446-72-0 (Genistein); 50-89-5 (Thymidine); 60-82-2 (Phloretin); 67256-21-7 (Hepatocyte Growth Factor); 70563-58-5 (herbimycin); 84477-87-2 (1-(5-Isoquinolinesulfonyl)-2-methylpiperazine); 9007-49-2 (DNA)

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); 0 (Culture Media, Conditioned); 0 (Culture Media, Serum-Free); 0 (Cytokines); 0 (Enzyme Inhibitors); 0 (Fibroblast Growth Factor, Basic); 0 (Growth Substances); 0 (Interleukin-1); 0 (Quinones); **0 (Stem Cell Factor)**

L42 ANSWER 35 OF 109 MEDLINE
AN 1998117124 MEDLINE
DN 98117124
TI SCF and c-kit in mastocytosis--a Pandora's box holding more theories than proven facts [letter; comment].
CM Comment on: J Invest Dermatol 1997 May;108(5):792-6
AU Henz B M
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1998 Feb)** 110 (2) 186-7.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Commentary
Letter

LA English
FS Cancer Journals; Priority Journals
EM 199805
CT Check Tags: Human
Adult
Child
***Mastocytosis: ME, metabolism**
*Models, Biological
***Proto-Oncogene Protein c-kit: ME, metabolism**
***Stem Cell Factor: ME, metabolism**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit); 0 (Stem Cell Factor)**

L42 ANSWER 36 OF 109 MEDLINE
AN 1998111342 MEDLINE
DN 98111342
TI Piebaldism with deafness: molecular evidence for an expanded syndrome.
AU Spritz R A; Beighton P
CS Department of Medical Genetics, School of Medicine, University of Wisconsin, Madison 53706, USA.
NC AR-39892 (NIAMS)
SO AMERICAN JOURNAL OF MEDICAL GENETICS, **(1998 Jan 6)** 75 (1) 101-3.
Journal code: 3L4. ISSN: 0148-7299.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
AB In a South African girl of Xhosa stock with severe piebaldism and profound congenital sensorineural deafness we identified a novel missense substitution at a highly conserved residue in the intracellular kinase domain of the KIT proto-oncogene, R796G. Though auditory anomalies have been observed in mice with dominant white spotting (W) due to KIT mutations, deafness is not typical in human piebaldism. Thus, the occurrence of sensorineural deafness in this patient extends considerably the phenotypic range of piebaldism due to KIT gene mutation in humans and tightens the clinical similarity between piebaldism and the various forms of Waardenburg syndrome.
CT Check Tags: Case Report; Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Amino Acid Substitution: GE, genetics
Arginine: GE, genetics
Child
Glycine: GE, genetics
*Hearing Disorders: CN, congenital
*Hearing Disorders: GE, genetics
***Piebaldism: GE, genetics**
Point Mutation
Pregnancy
***Proto-Oncogene Protein c-kit: GE, genetics**
Syndrome
RN 56-40-6 (Glycine); 7004-12-8 (Arginine)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 37 OF 109 MEDLINE
AN 1998101646 MEDLINE
DN 98101646
TI MAP kinase links the transcription factor Microphthalmia to c-Kit signalling in melanocytes.
AU Hemesath T J; Price E R; Takemoto C; Badalian T; Fisher D E
CS Division of Pediatric Hematology/Oncology, Children's Hospital and Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
SO NATURE, **(1998 Jan 15)** 391 (6664) 298-301.
Journal code: NSC. ISSN: 0028-0836.
CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199804
AB Germline mutations at loci encoding the transcription factor Microphthalmia (Mi), the cytokine receptor c-Kit, or its ligand Steel factor (Sl) result in strikingly similar defects in mast cell and melanocyte development. Here we describe a biochemical link between Kit signalling and the activity of Mi. Stimulation of melanoma cells with Sl results in activation of MAP kinase, which in turn phosphorylates Mi at a consensus target serine. This phosphorylation upregulates Mi transactivation of the tyrosinase pigmentation gene promoter. In addition to modulating pigment production, such signalling may regulate the expression of genes essential for melanocyte survival and development. The pathway represents a new application of the general MAP kinase machinery in transducing a signal between a tissue-specific receptor at the cell surface and a tissue-specific transcription factor in the nucleus.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Ca(2+)-Calmodulin Dependent Protein Kinase: AI, antagonists & inhibitors
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
DNA-Binding Proteins: GE, genetics
*DNA-Binding Proteins: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
Flavones: PD, pharmacology
***Melanocytes: ME, metabolism**
Mutagenesis, Site-Directed
Phosphorylation
Protein-Serine-Threonine Kinases: AI, antagonists & inhibitors
***Proto-Oncogene Protein c-kit: ME, metabolism**
Serine: ME, metabolism
***Signal Transduction**
Tumor Cells, Cultured
RN 56-45-1 (Serine)
CN EC 2.7.10 (Protein-Serine-Threonine Kinases); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.10.- (MEK kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (DNA-Binding Proteins); 0 (Enzyme Inhibitors); 0 (Flavones); 0 (Mi protein); 0 (PD 98059)

L42 ANSWER 38 OF 109 MEDLINE
AN 1998034982 MEDLINE
DN 98034982
TI Interleukin-9 is involved in host protective immunity to intestinal nematode infection.
AU Faulkner H; Humphreys N; Renauld J C; Van Snick J; Grencis R
CS School of Biological Sciences, University of Manchester, GB.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, **(1997 Oct)** 27 (10) 2536-40. Journal code: EN5. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802
AB Murine studies have demonstrated that, as with other nematodes, infection with the intestinal nematode Trichinella spiralis is associated with a pronounced intestinal mastocytosis, eosinophilia and an elevation in serum levels of total IgE. Both interleukin (IL)-4 and IL-5 are clearly important in the generation of IgE responses and eosinophilia, respectively, but the control of mucosal mastocytosis in vivo is not as well defined. Mucosal mast cells appear to be particularly important with regard to T. spiralis infections as there is good evidence to suggest their involvement in expulsion of the parasite from the host. In this study we examined the effect of the overproduction of the Th2 cytokine IL-9 on infection with this nematode. We demonstrate that naive IL-9-transgenic mice have an intense intestinal mastocytosis and high

serum levels of mouse mast cell protease-1. Moreover, upon infection high titers of parasite-specific IgG1 were observed with a heightened mast cell response, which was associated with the rapid expulsion of T. spiralis from the gut. Furthermore, as depression of this mast cell response, using anti-c-kit antibodies, resulted in the inability of these mice to expel the parasite, this study clearly demonstrates an activity of IL-9 on mucosal mastocytosis and the host protective immune response in vivo.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Biological Markers
Feces: PS, parasitology
Host-Parasite Relations
Immunity, Natural
Interleukin-9: GE, genetics
*Interleukin-9: PH, physiology
Interleukin-9: SE, secretion
Intestinal Diseases, Parasitic: CO, complications
Intestinal Diseases, Parasitic: EN, enzymology
*Intestinal Diseases, Parasitic: IM, immunology
Mastocytosis: EN, enzymology
***Mastocytosis: ET, etiology**
Mice
Mice, Transgenic
Proto-Oncogene Protein c-kit: PH, physiology
Serine Endopeptidases: BL, blood
Stem Cell Factor: PH, physiology
*Th2 Cells: IM, immunology
Th2 Cells: SE, secretion
*Trichinella spiralis: IM, immunology
Trichinosis: CO, complications
Trichinosis: EN, enzymology
*Trichinosis: IM, immunology

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 3.4.21 (Serine Endopeptidases); EC 3.4.21.39 (chymase); 0 (Biological Markers); 0 (Interleukin-9); **0 (Stem Cell Factor)**

L42 ANSWER 39 OF 109 MEDLINE
AN 1998025885 MEDLINE
DN 98025885
TI Overexpression of human stem cell factor impairs melanocyte, mast cell, and thymocyte development: a role for receptor tyrosine kinase-mediated mitogen activated protein kinase activation in cell differentiation.
AU Kapur R; Everett E T; Uffman J; McAndrews-Hill M; Cooper R; Ryder J; Vik T; Williams D A
CS Department of Pediatrics, James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, USA.
NC RO1 DK 48605 (NIDDK)
SO BLOOD, **(1997 Oct 15)** 90 (8) 3018-26.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199801
AB Stem cell factor (SCF) is synthesized as both soluble (S) and membrane-associated (MA) proteins. Indirect insight into the function of MA and S isoforms of SCF has come from studies performed in Steel (Sl) mutant mice. However, the physiologic role(s) of these two isoforms remain unknown. In an attempt to better understand the in vivo role of c-kit/SCF interactions on various cell lineages, transgenic mice were generated that overexpress MA isoform of human SCF (hSCF). In murine cells, hSCF behaves as an antagonist to normal SCF function, due to interference with the interaction between endogenous murine SCF and its receptor, c-kit, encoded by the dominant white spotting (W) gene. Mice expressing the hSCF transgene display a variety of phenotypic abnormalities, which are accentuated when combined with W alleles. Here we show that mice homozygous for the hSCF transgene demonstrate a coat color deficiency seen

in some mice homozygous for mild W alleles. Specifically, homozygous hSCF transgenic mice (hSCF220) display a pronounced forehead blaze, with additional white spots over the cervical region, as well as a very large belly spot. Doubly heterozygous animals that carry both a mutated W allele and the hSCF transgene also display an unusual pigment defect and a dramatic reduction in the number of dermal mast cells. Furthermore, overexpression of MA hSCF in the thymus results in abnormal thymocyte differentiation and proliferation, which is associated with reduced mitogen activated protein (MAP) kinase activation. Thus, MAP kinase activation by a receptor tyrosine kinase, such as c-kit, may be critical for the differentiation of thymocytes in vivo.

CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
***Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism**
*Cell Differentiation
Cell Separation
Enzyme Activation
Flow Cytometry
*Mast Cells: DE, drug effects
***Melanocytes: DE, drug effects**
Mice
Mice, Inbred C3H
Mice, Inbred C57BL
Mice, Mutant Strains
Mice, Transgenic
Proto-Oncogene Protein c-kit: ME, metabolism
***Receptor Protein-Tyrosine Kinases: ME, metabolism**
Skin: CY, cytology
***Stem Cell Factor: BI, biosynthesis**
Stem Cell Factor: PD, pharmacology
T-Lymphocyte Subsets: CY, cytology
*Thymus Gland: CY, cytology
Thymus Gland: DE, drug effects
CN EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); **0 (Stem Cell Factor)**

L42 ANSWER 40 OF 109 MEDLINE
AN 1998025871 MEDLINE
DN 98025871
TI Diamine oxidase-gold ultrastructural localization of histamine in human skin biopsies containing mast cells stimulated to degranulate in vivo by exposure to recombinant human stem cell factor.
AU Dvorak A M; Costa J J; Morgan E S; Monahan-Earley R A; Galli S J
CS Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215, USA.
NC AI-33372 (NIAID)
PO1-HL-56383 (NHLBI)
SO BLOOD, **(1997 Oct 15)** 90 (8) 2893-900.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB Stem cell factor (SCF) has a major role in hematopoiesis and in the regulation of mast cell development and function. For example, recombinant human SCF (rhSCF) can induce the development of human mast cells from precursor cells in vitro, stimulate mediator release from human skin mast cells in vitro, and promote both the development and functional activation of human skin mast cells in vivo. In the present study, we used a new ultrastructural enzyme-affinity method, employing diamine oxidase (DAO)-conjugated gold particles (DAO-gold), to detect histamine in skin biopsies obtained from patients with breast carcinomas who were receiving daily subcutaneous (SC) injections of rhSCF in a phase I study of this cytokine. We examined control biopsies obtained at sites remote from rhSCF

injection as well as biopsies of rhSCF-injected skin that were obtained within 2 hours and 30 minutes of the SC injection of rhSCF at that site. The rhSCF-injected sites (which clinically exhibited a wheal-and-flare response), but not the control sites, contained mast cells undergoing regulated secretion by granule extrusion. The DAO-gold-affinity method detected histamine in electron-dense granules of mast cells in control and injected skin biopsies; however, the altered matrix of membrane-free, extruded mast cell granules was largely unreactive with DAO-gold. Notably, DAO-gold bound strongly to fibrin deposits and collagen fibers that were adjacent to degranulated mast cells. These findings represent the first morphologic evidence of histamine secretion by classical granule exocytosis in human mast cells in vivo.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
***Amine Oxidase (Copper-Containing): ME, metabolism**
Biopsy
*Cell Degranulation
Cell Degranulation: DE, drug effects
Cytoplasmic Granules: UL, ultrastructure
Fibrin: AN, analysis
*Gold Colloid
*Histamine: AN, analysis
Histamine Release
Mast Cells: DE, drug effects
*Mast Cells: PH, physiology
Mast Cells: SE, secretion
Mast Cells: UL, ultrastructure
Recombinant Proteins: PD, pharmacology
***Skin: UL, ultrastructure**
***Stem Cell Factor: PD, pharmacology**
RN 51-45-6 (Histamine); 9001-31-4 (Fibrin)
CN EC 1.4.3.6 (Amine Oxidase (Copper-Containing)); 0 (Gold Colloid); 0 (Recombinant Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 41 OF 109 MEDLINE
AN 97457016 MEDLINE
DN 97457016
TI Proto-oncogene c-kit expression in malignant melanoma: protein loss with tumor progression.
AU Montone K T; van Belle P; Elenitsas R; Elder D E
CS Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia 19104, USA.. kathy_montone@path1a.med.upenn.edu
NC 2P01 CA25874-16 (NCI)
SO MODERN PATHOLOGY, **(1997 Sep)** 10 (9) 939-44.
Journal code: PTH. ISSN: 0893-3952.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
AB The c-kit gene encodes a transmembrane receptor that has tyrosine kinase activity. c-kit plays a role in hematopoiesis, gametogenesis, and melanogenesis. c-kit is found in melanocytes, and there is evidence that expression is lost in melanoma. We studied 85 melanocytic lesions for c-kit by immunohistochemical techniques using a monoclonal antibody. The lesions included banal nevi, junctional and compound nevi with melanocytic dysplasia, nontumorigenic radial growth phase melanoma, tumorigenic vertical growth phase melanoma, and metastatic melanoma. We found intense membrane staining in normal melanocytes and mast cells. Staining in compound nevi was strongest in junctional and superficial dermal components, whereas dermal nevi showed weak reactivity. Dysplastic nevi stained strongly, particularly in junctional cells. In melanoma, strong reactivity was most prominent in radial growth phase disease, but there was little or no staining in vertical growth phase and metastatic melanomas. In summary, c-kit protein is expressed in normal melanocytes,

benign nevi, dysplastic nevi and nontumorigenic melanoma, but expression is lost in tumorigenic primary melanomas and metastases. The role of c-kit loss in advanced melanoma requires additional investigation.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Disease Progression
Immunohistochemistry
Melanocytes: ME, metabolism
*Melanoma: ME, metabolism
Models, Biological
*Nevus: ME, metabolism
***Proto-Oncogene Protein c-kit: ME, metabolism**
***Skin Neoplasms: ME, metabolism**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 42 OF 109 MEDLINE
AN 97411638 MEDLINE
DN 97411638
TI Clinical, pathological, and etiologic aspects of acquired dermal melanocytosis.
AU Mizoguchi M; Murakami F; Ito M; Asano M; Baba T; Kawa Y; Kubota Y
CS Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan.
SO PIGMENT CELL RESEARCH, **(1997 Jun)** 10 (3) 176-83.
Journal code: PIG. ISSN: 0893-5785.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
AB To study the pathogenesis of acquired dermal melanocytosis (ADM), we reviewed the clinical, immunohistochemical, and ultrastructural features of 34 cases (female, 33, and male, 1) of ADM. The patients' ages at onset ranged from 8 to 51 years and averaged 26.8 +/- 12.7 years. There was a positive family history. Gray-brown macules were mostly recognized on the face. Not only active dermal melanocytes but also non-pigmented c-KIT- and TRP-2-positive immature melanocytes were detected in the dermis. Taken together those clinical and histological findings, activation of pre-existing immature melanocytes by sunlight, estrogen, and/or progesterone, and some other factors, may be the most likely mode of the development of ADM. Moreover, using cultured murine neural crest cells as a model of c-KIT-positive immature melanocytes, we confirmed that endothelin-1, which is produced and secreted by keratinocytes after UV-irradiation, affects melanocytes and accelerated melanogenesis.

CT Check Tags: Animal; Female; Human; Male
Adult
Age of Onset
Biological Markers
Cells, Cultured
Child
Dopa: AN, analysis
Endothelin-1: PD, pharmacology
Infant
Intramolecular Oxidoreductases: AN, analysis
Japan: EP, epidemiology
Melanocytes: DE, drug effects
***Melanocytes: PA, pathology**
Melanocytes: RE, radiation effects
Melanocytes: UL, ultrastructure
***Melanosis**
Melanosis: EP, epidemiology
Melanosis: ET, etiology
Melanosis: GE, genetics
Mice
Middle Age
Neural Crest: CY, cytology
Proto-Oncogene Protein c-kit: AN, analysis

Sex Hormones: PH, physiology
Skin: PA, pathology
Sunlight: AE, adverse effects
RN 63-84-3 (Dopa)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 5.3 (Intramolecular Oxidoreductases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (Biological Markers); 0 (Endothelin-1); 0 (Sex Hormones)

L42 ANSWER 43 OF 109 MEDLINE
AN 97385080 MEDLINE
DN 97385080
TI Role of mast cell and stem cell factor in **hyperpigmented** mycosis fungoides [letter].
AU Yamamoto T; Katayama I; Nishioka K
SO BLOOD, **(1997 Aug 1)** 90 (3) 1338-40.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Letter
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199710
EW 19971005
CT Check Tags: Female; Human; Male
Acanthosis Nigricans: BL, blood
Acanthosis Nigricans: ET, etiology
***Acanthosis Nigricans: PA, pathology**
Cytokines: SE, secretion
Histamine: BL, blood
*Mast Cells: PH, physiology
Middle Age
Mycosis Fungoides: BL, blood
Mycosis Fungoides: CO, complications
*Mycosis Fungoides: PA, pathology
*Neoplasm Proteins: PH, physiology
Pruritus: ET, etiology
Pruritus: PA, pathology
Skin Neoplasms: CO, complications
***Skin Neoplasms: PA, pathology**
Skin Pigmentation: PH, physiology
***Stem Cell Factor: PH, physiology**
RN 51-45-6 (Histamine)
CN 0 (Cytokines); 0 (Neoplasm Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 44 OF 109 MEDLINE
AN 97342667 MEDLINE
DN 97342667
TI Melanocyte development in vivo and in neural crest cell cultures: crucial dependence on the Mitf basic-helix-loop-helix-zipper transcription factor.
AU Opdecamp K; Nakayama A; Nguyen M T; Hodgkinson C A; Pavan W J; Arnheiter H
CS Laboratory of Developmental Neurogenetics, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO DEVELOPMENT, **(1997 Jun)** 124 (12) 2377-86.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
AB The more than 20 different Mitf mutations in the mouse are all associated with deficiencies in neural crest-derived melanocytes that range from minor functional disturbances with some alleles to complete absence of mature melanocytes with others. In the trunk region of wild-type embryos, Mitf-expressing cells that coexpressed the melanoblast marker Dct and the tyrosine kinase receptor Kit were found in the dorsolateral neural crest migration pathway. In contrast, in embryos homozygous for an Mitf allele

encoding a non-functional Mitf protein, Mitf-expressing cells were extremely rare, no Dct expression was ever found, and the number of Kit-expressing cells was much reduced. Wild-type neural crest cell cultures rapidly gave rise to cells that expressed Mitf and coexpressed Kit and Dct. With time in culture, Kit expression was increased, and pigmented, dendritic cells developed. Addition of the Kit ligand Mgf or endothelin 3 or a combination of these factors all rapidly increased the number of Dct-positive cells. Cultures from Mitf mutant embryos initially displayed Mitf-positive cells similar in numbers and Kit-expression as did wild-type cultures. However, Kit expression did not increase with time in culture and the mutant cells never responded to Mgf or endothelin 3, did not express Dct, and never showed pigment. In fact, even Mitf expression was rapidly lost. The results suggest that Mitf first plays a role in promoting the transition of precursor cells to melanoblasts and subsequently, by influencing Kit expression, melanoblast survival.

CT Check Tags: Animal
Amino Acid Sequence
Cell Differentiation: GE, genetics
Cells, Cultured
DNA-Binding Proteins: DE, drug effects
*DNA-Binding Proteins: PH, physiology
Embryo: PH, physiology
Endothelin-3: PD, pharmacology
*Gene Expression Regulation, Developmental
Isomerases: GE, genetics
Melanocytes: DE, drug effects
***Melanocytes: PH, physiology**
Mice
Mice, Inbred C3H
Mice, Inbred C57BL
Molecular Sequence Data
Mutation
*Neural Crest: CY, cytology
*Neural Crest: EM, embryology
Proto-Oncogene Protein c-kit: GE, genetics
Stem Cell Factor: PD, pharmacology

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 5. (Isomerases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (DNA-Binding Proteins); 0 (Endothelin-3); 0 (Mi protein); **0 (Stem Cell Factor)**

L42 ANSWER 45 OF 109 MEDLINE
AN 97311595 MEDLINE
DN 97311595
TI C-kit mutations and mast cell disorders. A model of activating mutations of growth factor receptors.
AU Pignon J M
CS Service d'Hematologie Biologique, Hopital Henri Mondor, Creteil, France.
SO HEMATOLOGY AND CELL THERAPY, **(1997 Apr)** 39 (2) 114-6. Ref: 14
Journal code: CKM. ISSN: 1430-2772.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199709
AB Mastocytosis are a group of diseases characterized by abnormal proliferation of mast cells. Various forms are observed in respect to the organ system involving, clinical manifestations, and association with hematological disorders. The c-kit proto-oncogene encodes for a receptor tyrosine kinase, which plays a crucial role in hematopoiesis, especially in mast cell growth and differentiation. Mutations in the tyrosine kinase domain of c-kit have been reported in murine and human malignant cell lines, and more recently in some cases of human mast cell diseases. The biochemical and clinical aspects of these mutations are reviewed with special emphasis on the experiments which demonstrate their role in

oncogenesis and mast cell proliferation.
CT Check Tags: Animal; Human
*Gene Expression Regulation
Mastocytosis: ET, etiology
***Mastocytosis: GE, genetics**
Mastocytosis: PA, pathology
Mice
*Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
Proto-Oncogene Protein c-kit: ME, metabolism
Receptors, Growth Factor: AG, agonists
***Receptors, Growth Factor: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Receptors, Growth Factor)

L42 ANSWER 46 OF 109 MEDLINE
AN 97276859 MEDLINE
DN 97276859
TI Conditioned media obtained from a human mastocytosis cell strain induce mast cells expressing chymase but not tryptase from human progenitors.
AU Li L; Krilis S A
CS School of Medicine, University of New South Wales and Department of Immunology, Allergy and Infectious Disease, St. George Hospital, Kogarah, Australia.
SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, **(1997 May-Jul)** 113 (1-3) 289-90.
Journal code: BJ7. ISSN: 1018-2438.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
AB Human mast cells (MC) were derived from umbilical cord blood and bone marrow progenitors cultured in the presence of a conditioned medium from a human mastocytosis cell strain and recombinant human kit ligand (rhKL). KL induced MC of predominantly two immunophenotypes, MC(T) and MC(TC). In contrast, the conditioned medium induced MC subtypes MC(TC) and a third subtype, MC(C), positive for chymase but negative for tryptase. This study clearly demonstrates that a third type of MC, MC(C), can be induced in vitro from normal human progenitors.
CT Check Tags: Human; Support, Non-U.S. Gov't
*Bone Marrow: CY, cytology
Cells, Cultured
Culture Media, Conditioned
*Fetal Blood: CY, cytology
***Hematopoietic Stem Cells: EN, enzymology**
*Mast Cells: EN, enzymology
***Mastocytosis: PP, physiopathology**
***Serine Endopeptidases: BI, biosynthesis**
Stem Cell Factor: PD, pharmacology
CN EC 3.4.21 (Serine Endopeptidases); EC 3.4.21.39 (chymase); EC 3.4.21.59 (tryptase); 0 (Culture Media, Conditioned); **0 (Stem Cell Factor)**

L42 ANSWER 47 OF 109 MEDLINE
AN 97276824 MEDLINE
DN 97276824
TI c-kit mutation in a population of patients with mastocytosis.
AU Nagata H; Okada T; Worobec A S; Semere T; Metcalfe D D
CS Department of Otolaryngology, Chiba University School of Medicine, Japan.
SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, **(1997 May-Jul)** 113 (1-3) 184-6.
Journal code: BJ7. ISSN: 1018-2438.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199707
AB The c-kit Asp816Val activating mutation is found in all patients with mastocytosis with an associated hematologic disorder, and at least in a subset of patients with indolent mastocytosis. The case of an 11-month-old child is presented who was categorized as having indolent mastocytosis, and where the Asp816Val mutation was identified in lesional skin, but not in bone marrow or in peripheral blood mononuclear cell populations. The significance of these findings is discussed.
CT Check Tags: Human; Male
Infant
***Mastocytosis: GE, genetics**
*Mutation
***Proto-Oncogene Protein c-kit: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 48 OF 109 MEDLINE
AN 97180810 MEDLINE
DN 97180810
TI A new c-kit mutation in a case of aggressive mast cell disease.
AU Pignon J M; Giraudier S; Duquesnoy P; Jouault H; Imbert M; Vainchenker W; Vernant J P; Tulliez M
CS Service d'Hematologie Biologique, Hopital Henri Mondor, Creteil, France.
SO BRITISH JOURNAL OF HAEMATOLOGY, **(1997 Feb)** 96 (2) 374-6.
Journal code: AXC. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199705
AB Systemic mast cell disease (SMCD) is a disorder characterized by a mast cell proliferation in various tissues. Mast cells express the c-kit proto-oncogene. A few cases of c-kit mutations have been described in SMCD. We report an aggressive SMCD in a patient who presented with a bone marrow infiltration by abnormal mast cells. Molecular studies of mast cell DNA and RNA revealed a new c-kit heterozygous mutation (Asp820Gly). This mutation leads to a drastic amino-acid change and is located close to the highly oncogenic Asp816Val. These findings suggest that the Asp820Gly has a potential role in c-kit activation.
CT Check Tags: Case Report; Human; Male
Adult
Fatal Outcome
***Mastocytosis: GE, genetics**
*Mutation
Polymerase Chain Reaction
***Proto-Oncogene Protein c-kit: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 49 OF 109 MEDLINE
AN 97164704 MEDLINE
DN 97164704
TI Multiple roles for endothelin in melanocyte development: regulation of progenitor number and stimulation of differentiation.
AU Reid K; Turnley A M; Maxwell G D; Kurihara Y; Kurihara H; Bartlett P F; Murphy M
CS The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, Victoria, Australia.
NC NS16115 (NINDS)
SO DEVELOPMENT, **(1996 Dec)** 122 (12) 3911-9.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
EW 19970501
AB Melanocytes in the skin are derived from the embryonic neural crest.

Recently, mutations in endothelin 3 and the endothelin receptor B genes have been shown to result in gross pigment defects, indicating that this signalling pathway is required for melanocyte development. We have examined the effects of endothelins on melanocyte progenitors in cultures of mouse neural crest. Firstly, they stimulate an increase in progenitor number and act synergistically with another factor, Steel factor, in the survival and proliferation of the progenitors. These findings are consistent with findings from mice with natural mutations in the endothelin receptor B gene, which show an early loss of melanocyte progenitors. Secondly, endothelins induce differentiation of the progenitors into fully mature pigmented melanocytes. This finding is consistent with the expression of endothelins in the skin of mice at the initiation of pigmentation. The melanocytes generated in endothelin-treated cultures also become responsive to alpha melanocyte-stimulating hormone, which then acts to regulate the activity of the pigmentation pathway. These findings indicate two key roles for endothelin in melanocyte development: regulation of expansion of the progenitor pool and differentiation of progenitors into mature melanocytes.

CT Check Tags: In Vitro; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
alpha-MSH: PD, pharmacology
Cell Count
Cell Differentiation
Drug Interactions
Endothelin-1: ME, metabolism
Endothelin-1: PD, pharmacology
Endothelin-3: ME, metabolism
Endothelin-3: PD, pharmacology
Endothelins: ME, metabolism
*Endothelins: PD, pharmacology
Hair Color: GE, genetics
Melanocytes: CY, cytology
***Melanocytes: DE, drug effects**
*Neural Crest: CY, cytology
Pigmentation: DE, drug effects
Protein Binding
Receptors, Endothelin: IP, isolation & purification
***Skin: EM, embryology**
Stem Cell Factor: PD, pharmacology
Stem Cells: CY, cytology
***Stem Cells: DE, drug effects**
Tissue Culture
Tissue Distribution

RN 581-05-5 (alpha-MSH)

CN 0 (Endothelin-1); 0 (Endothelin-3); 0 (Endothelins); 0 (Receptors, Endothelin); **0 (Stem Cell Factor)**

L42 ANSWER 50 OF 109 MEDLINE

AN 97158708 MEDLINE

DN 97158708

TI Long-range genomic rearrangements upstream of Kit dysregulate the developmental pattern of Kit expression in W57 and Wbanded mice and interfere with distinct steps in melanocyte development.

AU Kluppel M; Nagle D L; Bucan M; Bernstein A

CS Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada.

NC HD 28410 (NICHD)

SO DEVELOPMENT, **(1997 Jan)** 124 (1) 65-77.
Journal code: ECW. ISSN: 0950-1991.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199705

AB Mutations in the murine dominant white spotting (W) locus cause pleiotropic developmental defects that affect hematopoietic cells,

melanocytes, germ cells and the interstitial cells of Cajal in the gut. W mutations either alter the coding sequence of the Kit receptor tyrosine kinase, resulting in a receptor with impaired kinase activity, or affect Kit expression. Here we describe the molecular and cell-type-specific developmental defects of two of the latter class of regulatory W alleles, W57 and Wbanded(bd). In both mutants, the temporal and spatial patterns of Kit expression are dysregulated during embryogenesis and in adult animals. In Wbd mice, ectopic expression of Kit in the dermatome of the somites at days 10.8 and 11.8 of development seemed to interfere with melanoblast development. In contrast, the W57 allele leads to an intrinsic pigmentation defect by downregulating developmental Kit expression in trunk melanoblasts, but not melanoblasts around the otic vesicle. Both mutations affect transcriptional initiation of the Kit gene. The W57 allele is associated with a 80 kb deletion 5' of the Kit-coding region while Wbd is associated with a 2.8 Mb genomic inversion of chromosome 5 with the distal breakpoint between Kit and the platelet-derived growth factor receptor alpha (Pdgfra) gene, and the proximal breakpoint between the genes for the GABA receptor beta 1 (Gabrb1) and the Tec tyrosine kinase, juxtaposing the Kit and Tec tyrosine kinase genes. Neither W57 nor Wbd affect genomic sequences previously suggested in in vitro experiments to control cell-type-specific expression of Kit. These results link specific mechanisms of cellular and developmental defects to long-range genomic rearrangements that positively and negatively affect Kit transcription in different cell lineages as well as in different subpopulations of the same lineage.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alleles
Bone Marrow: CY, cytology
Cells, Cultured
*Chromosome Mapping
DNA Primers
Fetal Development
*Gene Rearrangement
*Genes, Regulator
Genetic Markers
Gestational Age
Inversion (Genetics)
Mast Cells: CY, cytology
Melanocytes: CY, cytology
***Melanocytes: PH, physiology**
Mice
Mice, Inbred C3H
Mice, Inbred C57BL
Mice, Inbred Strains
Mice, Mutant Strains
Polymerase Chain Reaction
Proto-Oncogene Protein c-kit: BI, biosynthesis
***Proto-Oncogene Protein c-kit: GE, genetics**
Receptor Protein-Tyrosine Kinases: BI, biosynthesis
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptors, GABA: GE, genetics
Receptors, Platelet-Derived Growth Factor: GE, genetics
Sequence Deletion
Transcription, Genetic

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); EC 2.7.11.- (Receptor, Platelet-Derived Growth Factor alpha); EC 2.7.11.- (Receptors, Platelet-Derived Growth Factor); 0 (DNA Primers); 0 (Genetic Markers); 0 (Receptors, GABA)

L42 ANSWER 51 OF 109 MEDLINE
AN 97115983 MEDLINE
DN 97115983
TI Enforced c-KIT expression renders highly metastatic human melanoma cells susceptible to stem cell factor-induced apoptosis and inhibits their tumorigenic and metastatic potential.

AU Huang S; Luca M; Gutman M; McConkey D J; Langley K E; Lyman S D; Bar-Eli M
CS Department of Cell Biology, The University of Texas MD Anderson Cancer Center, Houston 77030, USA.
NC CA 41524 (NCI)
CA64137 (NCI)
SO ONCOGENE, **(1996 Dec 5)** 13 (11) 2339-47.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199703
AB Expression of the tyrosine-kinase receptor encoded by the c-KIT proto-oncogene progressively decreases during local tumor growth and invasion of human melanomas. To provide direct evidence that c-KIT plays a role in metastasis of human melanoma, we transfected the c-KIT gene into the c-KIT negative highly metastatic human melanoma cell line A375SM and subsequently analysed its tumorigenic and metastatic potential. A375SM parental cells, A375SM-NOT (neo, control), and A375SM-KIT-positive cells were injected s.c. and i.v. into nude mice. A375SM-KIT cells produced significantly slower growing s.c. tumors and fewer lung metastases than control cells. Exposure of c-KIT-positive melanoma cells in vitro and in vivo to stem cell factor (SCF), the ligand for c-KIT, triggered apoptosis of these cells but not of c-KIT-negative melanoma cells or normal melanocytes. Since SCF is produced by keratinocytes and other dermal cells in the skin, these results suggest that the loss of c-KIT receptor expression may allow malignant melanoma cells to escape SCF/c-KIT-mediated apoptosis, hence contributing to tumor growth and eventually metastasis. The antitumor and antimetastatic properties of SCF may be useful in treating human melanomas in early stages.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Apoptosis
*Lung Neoplasms: SC, secondary
Melanoma: GE, genetics
*Melanoma: ME, metabolism
Melanoma: PA, pathology
*Melanoma: SC, secondary
Mice
Mice, Inbred BALB C
Mice, Nude
Neoplasm Proteins: GE, genetics
*Neoplasm Proteins: ME, metabolism
Neoplasm Transplantation
Phenotype
Proto-Oncogene Protein c-kit: GE, genetics
***Proto-Oncogene Protein c-kit: ME, metabolism**
RNA, Messenger: ME, metabolism
Skin Neoplasms: GE, genetics
***Skin Neoplasms: ME, metabolism**
Skin Neoplasms: PA, pathology
Stem Cell Factor: ME, metabolism
***Stem Cell Factor: PD, pharmacology**
Transfection
Tumor Cells, Cultured
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Neoplasm Proteins); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L42 ANSWER 52 OF 109 MEDLINE
AN 97062686 MEDLINE
DN 97062686
TI Neural and skin cell-specific expression pattern conferred by steel factor regulatory sequence in transgenic mice.
AU Yoshida H; Hayashi S; Shultz L D; Yamamura K; Nishikawa S; Nishikawa S; Kunisada T
CS Department of Molecular Genetics, Faculty of Medicine, Kyoto University,

Japan.
NC CA 20408 (NCI)
SO DEVELOPMENTAL DYNAMICS, **(1996 Oct)** 207 (2) 222-32.
Journal code: A9U. ISSN: 1058-8388.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U63649
EM 199704
AB We have produced transgenic mice expressing a lacZ reporter gene under the control of a fragment of a Steel factor (SLF). The function of this gene is essential for the development of hematopoietic cells, germ cells, melanocytes and pacemaker cells of the intestine. The expression of the transgene, containing 2 kb DNA 5' regulatory sequence, was restricted to neural and skin tissues in appropriate spatial and temporal pattern compared with endogenous SLF mRNA expression. This indicates that the regulatory elements necessary for the neural and skin specific expression are present in this 2 kb DNA sequence, although strong position-dependence of transgene expression was observed. As we could not detect transgene expression in hematopoietic tissues and germ cells after extending 10 kb upstream, elements important for these organs must reside in other regions. Our results indicate that neural crest derived enteric ganglion cells provide SLF to the neighboring pace maker cells expressing c-kit, the receptor for SLF. Cells expressing the transgene in the intestine are ganglion cells derived from neural crest since homozygosity for the lethal spotting (Is) mutation results in loss of such ganglion cells in transgenic mice. We have also shown that the dermal papillae of the hair follicle expresses the transgene, suggesting its roles to support the c-kit dependent growth and development of melanocytes in the hair follicle.
CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Base Sequence
Central Nervous System
Chloramphenicol O-Acetyltransferase: GE, genetics
Chloramphenicol O-Acetyltransferase: ME, metabolism
Digestive System: ME, metabolism
DNA
Genes, Reporter
In Situ Hybridization
Mice
Mice, Inbred C57BL
Mice, Inbred DBA
Mice, Transgenic
Molecular Sequence Data
Neurons: CY, cytology
*Neurons: ME, metabolism
Peripheral Nervous System
Proto-Oncogene Protein c-kit: ME, metabolism
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: ME, metabolism
*Regulatory Sequences, Nucleic Acid
Skin: CY, cytology
***Skin: ME, metabolism**
Stem Cell Factor: GE, genetics
***Stem Cell Factor: ME, metabolism**
Transgenes
RN 9007-49-2 (DNA)
CN EC 2.3.1.28 (Chloramphenicol O-Acetyltransferase); **EC 2.7.11.-(Proto-Oncogene Protein c-kit)**; 0 (Recombinant Fusion Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 53 OF 109 MEDLINE
AN 97029979 MEDLINE
DN 97029979

TI Mutations in the ligand-binding domain of the kit receptor: an uncommon site in human piebaldism.
AU Fleischman R A; Gallardo T; Mi X
CS Division of Hematology/Oncology, University of Kentucky, Lexington, USA.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1996 Nov)** 107 (5) 703-6.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199701
AB Heterozygous mutations in the gene for the Kit transmembrane receptor have been identified recently in human piebaldism and mouse "dominant spotting." Interestingly, all of the 14 known missense mutations that cause depigmentation in these species map to the tyrosine kinase domain of the receptor, whereas none have involved the extracellular ligand-binding domain. In an attempt to detect these uncommon mutations, we screened the nine exons encoding the extracellular portion of Kit for single-strand conformation polymorphisms (SSCP) in eight piebald subjects previously reported to be negative for kinase mutations. Four of these eight kindreds proved to carry novel mutations. The first mutation, found in two apparently unrelated probands with mild piebaldism and English ancestry, substitutes an arginine for a highly conserved cysteine at codon 136. This substitution disrupts a putative disulfide bond required for formation of the second Ig-like (D2) loop of the Kit ligand-binding domain. The second mutation, detected in a piebald kindred characterized by unusually limited depigmentation, substitutes a threonine for an alanine at codon 178, a site just proximal to conserved cysteines at codons 183 and 186. The third mutation, occurring in a kindred with more extensive depigmentation, is a novel four-base insertion in exon 2 that results in a proximal frameshift and premature termination. The data strongly suggest that piebaldism can result from missense mutations in the Kit ligand-binding domain, although the resulting phenotype may be milder than that observed for null or kinase mutations. The apparent clustering of these uncommon mutations at or near the conserved cysteines for the D2 Ig-like loop further suggests a critical role for this region in Kit receptor function.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Binding Sites
Codon
Heterozygote
Ligands
*Mutation
***Piebaldism: GE, genetics**
Polymorphism, Single-Stranded Conformational
***Proto-Oncogene Protein c-kit: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Codon); 0 (Ligands)

L42 ANSWER 54 OF 109 MEDLINE
AN 96400448 MEDLINE
DN 96400448
TI Ectopic c-kit expression affects the fate of melanocyte precursors in Patch mutant embryos.
AU Wehrle-Haller B; Morrison-Graham K; Weston J A
CS Institute of Neuroscience, University of Oregon, Eugene 97403-1254, USA.
NC DE-04316 (NIDCR)
SO DEVELOPMENTAL BIOLOGY, **(1996 Aug 1)** 177 (2) 463-74.
Journal code: E7T. ISSN: 0012-1606.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199612
AB The Patch (Ph) mutation in the mouse, a deletion that includes the gene for PDGFR alpha, is a recessive lethal that exhibits a dominant pigment

phenotype in heterozygotes. To assess whether the Ph mutation acts cell-autonomously or non-autonomously on melanocyte development, we have examined the melanogenic potential of neural crest populations from normal and mutant crest cells in vitro and the pattern of dispersal and survival of melanocyte precursors (MPs) in vivo. We report that trunk neural crest cells from homozygous Ph embryos give rise to pigmented melanocytes in vitro in response to Steel factor (SlF). In vivo, homozygous Ph embryos contain a subpopulation of crest-derived cells that express c-kit and tyrosinase-related protein-2 characteristic of MPs. These cells begin to migrate normally on the lateral crest migration pathway, but then fail to disperse in the dermal mesenchyme and subsequently disappear. Although dermal mesenchyme is adversely affected in Ph homozygotes, SlF mRNA expression by the cells of the dermatome is normal in Ph embryos when neural crest-derived MPs start to migrate on the lateral pathway. In contrast, mRNA for the SlF receptor, c-kit, was observed to be ectopically expressed in somites and lateral mesenchyme in embryos carrying the Ph mutation. Based on this ectopic expression of c-kit in Ph mutant embryos, and the observed distribution of SlF protein in normal and mutant embryos, we suggest that competition for limited amounts of SlF localized on the lateral neural crest migration pathway alters melanocyte dispersal and survival.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Base Sequence
Cell Movement
Cells, Cultured
Gene Deletion
Gene Expression Regulation, Developmental
Melanins: BI, biosynthesis
***Melanocytes: PH, physiology**
*Mice: EM, embryology
Mice, Inbred BALB C
Mice, Inbred C57BL
Molecular Sequence Data
Neural Crest: CY, cytology
Pregnancy
Proto-Oncogene Protein c-kit: AN, analysis
***Proto-Oncogene Protein c-kit: BI, biosynthesis**
Proto-Oncogene Protein c-kit: GE, genetics
RNA, Messenger: AN, analysis
Stem Cell Factor: PH, physiology
Stem Cells

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Melanins); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L42 ANSWER 55 OF 109 MEDLINE
AN 96362632 MEDLINE
DN 96362632
TI The expression of the c-kit receptor by epidermal melanocytes may be reduced in vitiligo.
AU Norris A; Todd C; Graham A; Quinn A G; Thody A J
CS Department of Dermatology, University of Newcastle upon Tyne, U.K.
SO BRITISH JOURNAL OF DERMATOLOGY, **(1996 Feb)** 134 (2) 299-306.
Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199612
AB The proto-oncogene c-kit encodes the transmembrane tyrosine kinase receptor that has a role in the growth regulation of various cell types including melanocytes. In the present study we have examined the expression of the c-kit protein in the skin of seven patients with vitiligo. Melanocytes positive for c-kit protein were observed in the basal layer in non-lesional skin and the mean number of 25.8 +/- 5.2 (per 200 basal cells) compared with that of 21.8 +/- 3.5 from six control

subjects. In perilesional skin there was a reduction in the numbers of c-kit positive melanocytes (6.7 +/- 2.6) and this was especially noticeable in six of the seven patients. Such a reduction was less obvious following staining with MEL-5 and in only two subjects were the numbers of melanocytes below the normal range. This suggests that the reduction in c-kit staining was the result of decreased expression of the protein rather than a loss of melanocytes. No melanocytes, positive for c-kit protein, or after staining with MEL-5, were identified in lesional skin although isolated tyrosinase-positive melanocytes were seen in one subject. There was no apparent change in the numbers of mast cells expressing c-kit protein and the intensity of staining in the dermis even in lesional skin was similar to that in the controls. These results demonstrate that c-kit protein is present on melanocytes in adult human skin and that in perilesional skin of some vitiligo patients there is a reduction in the numbers of melanocytes expressing this receptor. Whether this may contribute to the defective melanocyte growth and/or survival that occurs in vitiligo or whether it is a consequence of melanocyte damage remains to be seen.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Case-Control Studies
Cell Count
Epidermis: CH, chemistry
Immunoenzyme Techniques
***Melanocytes: CH, chemistry**
Middle Age
***Proto-Oncogene Protein c-kit: AN, analysis**
Skin: CH, chemistry
***Skin: PA, pathology**
***Vitiligo**
Vitiligo: PA, pathology

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 56 OF 109 MEDLINE
AN 96322767 MEDLINE
DN 96322767
TI CD88 antibodies specifically bind to C5aR on dermal CD117+ and CD14+ cells and react with a desmosomal antigen in human skin.
AU Werfel T; Zwirner J; Oppermann M; Sieber A; Begemann G; Drommer W; Kapp A; Gotze O
CS Department of Dermatology, Hannover Medical School, Germany.
SO JOURNAL OF IMMUNOLOGY, **(1996 Aug 15)** 157 (4) 1729-35.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199611
AB The expression of the C5aR (CD88) on human epidermal and dermal cells was studied with five anti-C5aR mAb directed to the N-terminal domain of the receptor. All mAb bound to suspended dermal CD117+ mast cells and to dermal CD14+ cells. The binding to CD14+ and CD117+ cells could be blocked by rC5a and by peptide EX-1 representing amino acid residues 1-31 of the C5aR. In acetone-fixed frozen or in paraformaldehyde-fixed, paraffin-embedded tissue, we detected a binding of the Abs to dermal perivascular cells and, additionally, to keratinocytes and dermal epithelial cells that could be blocked by EX-1. Immunoelectromicroscopy revealed a binding of anti-C5aR mAb to desmosomal regions in human epidermis. However, the following results indicate that CD88 mAb cross-react with epithelium in a specific way: 1) the binding to suspended epidermal cells and to the epidermal cell line HaCat could be blocked by EX-1 but not by rC5a; 2) FITC-labeled C5a bound to CD117+ and to CD14+ cells but not to epidermal cells; 3) C5a led to transient calcium fluxes in CD14+ and CD117+ dermal but not in epidermal cells; 4) C5aR mRNA was detectable by reverse transcription PCR in granulocytes but not in keratinocytes or in HaCat. Our results show that CD88 mAb are good tools

for the investigation of the C5aR on hemopoietic cells. Results with epithelial cells should be considered with caution, as the binding of CD88 mAb that were raised to a synthetic peptide sequence may be due to a cross-reactivity.

CT Check Tags: Human; Support, Non-U.S. Gov't
*Antibodies, Monoclonal: IM, immunology
Antigens, CD: BI, biosynthesis
Antigens, CD: GE, genetics
*Antigens, CD: IM, immunology
***Antigens, CD14: AN, analysis**
Base Sequence
*Desmosomes: IM, immunology
Epidermis: CY, cytology
Epidermis: IM, immunology
Keratinocytes: IM, immunology
Molecular Sequence Data
Polymerase Chain Reaction
***Proto-Oncogene Protein c-kit: AN, analysis**
Receptors, Complement: BI, biosynthesis
Receptors, Complement: GE, genetics
***Receptors, Complement: IM, immunology**
RNA, Messenger: BI, biosynthesis
Skin: CY, cytology
***Skin: IM, immunology**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (complement 5a receptor); 0 (Antibodies, Monoclonal); 0 (Antigens, CD); 0 (Antigens, CD14); 0 (Receptors, Complement); 0 (RNA, Messenger)

L42 ANSWER 57 OF 109 MEDLINE
AN 96287384 MEDLINE
DN 96287384
TI A 12-bp deletion (7818del12) in the c-kit protooncogene in a large Italian kindred with piebaldism.
AU Riva P; Milani N; Gandolfi P; Larizza L
CS Department of Biology and Genetics, University of Milan, Italy.
SO HUMAN MUTATION, **(1995)** 6 (4) 343-5.
Journal code: BRD. ISSN: 1059-7794.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Base Sequence
Infant, Newborn
Italy
Molecular Sequence Data
Mutation
Pedigree
***Piebaldism: GE, genetics**
***Proto-Oncogene Protein c-kit: GE, genetics**
*Sequence Deletion
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 58 OF 109 MEDLINE
AN 96281921 MEDLINE
DN 96281921
TI Recombinant human stem cell factor (kit ligand) promotes human mast cell and melanocyte hyperplasia and functional activation in vivo.
AU Costa J J; Demetri G D; Harrist T J; Dvorak A M; Hayes D F; Merica E A; Menchaca D M; Gringeri A J; Schwartz L B; Galli S J
CS Department of Pathology, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA.
NC CA/AI-72074 (NCI)
AI/GM-23990 (NIAID)
AI-31982 (NIAID)

+
SO JOURNAL OF EXPERIMENTAL MEDICINE, **(1996 Jun 1)** 183 (6) 2681-6.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199610
AB Stem cell factor (SCF), also known as mast cell growth factor, kit ligand, and steel factor, is the ligand for the tyrosine kinase receptor (SCFR) that is encoded by the c-kit proto-oncogene. We analyzed the effects of recombinant human SCF (r-hSCF, 5-50 micrograms/kg/day, injected subcutaneously) on mast cells and melanocytes in a phase I study of 10 patients with advanced breast carcinoma. A wheal and flare reaction developed at each r-hSCF injection site; by electron microscopy, most dermal mast cells at these sites exhibited extensive, anaphylactic-type degranulation. A 14-d course of r-hSCF significantly increased dermal mast cell density at sites distant to those injected with the cytokine and also increased both urinary levels of the major histamine metabolite, methyl-histamine, and serum levels of mast cell alpha-tryptase. Five subjects developed areas of persistent **hyperpigmentation** at r-hSCF injection sites; by light microscopy, these sites exhibited markedly increased epidermal melanization and increased numbers of melanocytes. The demonstration that r-hSCF can promote both the hyperplasia and the functional activation of human mast cells and melanocytes in vivo has implications for our understanding of the role of endogenous SCF in health and disease. These findings also indicate that the interaction between SCF and its receptor represents a potential therapeutic target for regulating the numbers and functional activity of both mast cells and cutaneous melanocytes.
CT Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Anaphylaxis
Biopsy
Breast Neoplasms: IM, immunology
Breast Neoplasms: PA, pathology
*Breast Neoplasms: TH, therapy
Dose-Response Relationship, Drug
Hyperplasia
Mast Cells: DE, drug effects
*Mast Cells: PA, pathology
Melanocytes: DE, drug effects
***Melanocytes: PA, pathology**
Neoplasm Staging
Recombinant Proteins: AE, adverse effects
Skin: PA, pathology
***Stem Cell Factor: AE, adverse effects**
CN 0 (Recombinant Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 59 OF 109 MEDLINE
AN 96213701 MEDLINE
DN 96213701
TI c-KIT receptor expression in cutaneous malignant melanoma and benign melanotic naevi.
AU Ohashi A; Funasaka Y; Ueda M; Ichihashi M
CS Department of Dermatalogy, Kobe University School of Medicine, Japan.
SO MELANOMA RESEARCH, **(1996 Feb)** 6 (1) 25-30.
Journal code: BJR. ISSN: 0960-8931.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
AB To investigate the role of c-KIT receptor in melanocytic tumour

development and progression, we analysed the expression and localization of c-KIT by immunohistochemistry and Western blotting. In contrast to the positive staining shown by melanocytes and naevus cells in the epidermis of common naevi (n=20), all dysplastic naevi (n=13) were negative, as were dermal melanocytic cells of blue naevi (n = 4) and common naevi (n = 26). Three out of four superficial spreading melanomas lost c-KIT expression both in the epidermal and dermal parts, while nodular melanomas showed no expression of c-KIT except in partially positive cells, and six out of seven metastatic melanomas were negative. In acral lentiginous melanomas (n = 8), in contrast to other types of melanoma, all cases with melanoma cells growing basally in the epidermis showed strong c-KIT positivity, but melanoma cells growing at the upper layers of the epidermis and vertically into the dermis lost c-KIT expression. Using the Western blot method on cultured pigment cells, human epidermal melanocytes, junctional naevus cells and one out of three metastatic melanoma cell lines showed 125 and 145 kDa bands corresponding to c-KIT, whereas dermal naevus cells did not. These results suggest that dysplastic naevi are distinct from ordinary naevi in terms of c-KIT expression and that basally growing cells in acral lentigenous melanomas could be at an initial stage of tumour progression, before c-KIT loss occurs.

CT Check Tags: Human
Blotting, Western
Cells, Cultured
Immunohistochemistry
Keratinocytes: UL, ultrastructure
Melanocytes: UL, ultrastructure
Melanoma: PA, pathology
*Melanoma: UL, ultrastructure
Nevus: PA, pathology
*Nevus: UL, ultrastructure
***Proto-Oncogene Protein c-kit: AN, analysis**
Reference Values
Skin: UL, ultrastructure
Skin Neoplasms: PA, pathology
***Skin Neoplasms: UL, ultrastructure**
Tumor Cells, Cultured

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 60 OF 109 MEDLINE
AN 96210349 MEDLINE
DN 96210349
TI KIT expression reveals a population of precursor melanocytes in human skin.
AU Grichnik J M; Ali W N; Burch J A; Byers J D; Garcia C A; Clark R E; Shea C R
CS Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.
NC 5T32AR07093-18 (NIAMS)
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1996 May)** 106 (5) 967-71.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199608
AB Human skin is believed to harbor a reservoir population of precursor melanocytes. It has been difficult to identify these putative cells experimentally, because they lack phenotypic features that define mature melanocytes. We have evaluated expression of the KIT tyrosine kinase receptor, which is critical for melanocyte development, as a possible marker of these cells. Sections of human skin were evaluated with single- and double-immunolabeling techniques. KIT-reactive dendritic cells were identified in the basal layer of the epithelia and were most numerous in the follicular infundibula and the rete ridges. These cells were located on the epithelial side of the basement membrane and lacked expression of cytokeratin and mast cell tryptase. The location of the KIT-reactive cells

was distinctly different from that of Langerhans cells (identified with anti-CD1a) or Merkel cells (identified with CAM 5.2). Within the epidermis and upper follicular infundibulum the majority of the KIT-reactive dendritic cells also coexpressed TRP-1, a marker present in differentiated melanocytes. In the deeper follicular regions, the coexpression of TRP-1 in the KIT-reactive cells was absent. Throughout the epidermis and follicle, however, the KIT-reactive cells coexpressed BCL-2, a marker known to be increased in melanocytes. Thus, KIT expression reveals a population of intraepithelial cells that have immunophenotypic characteristics of mature melanocytes within the upper epithelial regions, but lack the differentiated melanocytic phenotype within the deeper follicular regions. We propose that these KIT(+), BCL-2(+), and TRP-1(-) cells constitute a precursor melanocyte reservoir of human skin.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adult
Aged
Fluorescent Antibody Technique
***Melanocytes: CH, chemistry**
Middle Age
***Proto-Oncogene Protein c-kit: AN, analysis**
Skin: CH, chemistry
***Skin: CY, cytology**
***Stem Cells: CH, chemistry**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**

L42 ANSWER 61 OF 109 MEDLINE
AN 96205044 MEDLINE
DN 96205044
TI Distinct stages of melanocyte differentiation revealed by anlaysis of nonuniform pigmentation patterns.
AU Yoshida H; Kunisada T; Kusakabe M; Nishikawa S; Nishikawa S I
CS Department of Molecular Genetics, Faculty of Medicine, Kyoto University, Japan.
SO DEVELOPMENT, **(1996 Apr)** 122 (4) 1207-14.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199608
AB The injection of an antagonistic anti-murine c-kit monoclonal antibody ACK2 during mouse embryonic development produced three distinctive pigmentation patterns on the coat of the offspring. Pattern 1 consisted of pigmentation in craniofacial and caudal regions and was induced by an ACK2 injection between 9.5 and 11.5 days post coitum (dpc). In pattern 2, the entire coat was unpigmented and was induced by the injection at around 13.0 dpc. Pattern 3 consisted of pigmented patches spreading ventrolaterally from the dorsoanterior trunk regions towards the anterior and posterior directions and it was induced by ACK2 administered at 14.5-15.0 dpc. We investigated the embryological basis of these nonuniform pigmentation patterns to elucidate the process of melanoblast differentiation between lineage commitment and colonization into developing hair follicles. The results showed the following. (1) Melanocyte differentiation at the embryonic stage from 10.5 to 12.5 dpc progresses in a spatially nonuniform fashion, being faster in the craniofacial and caudal regions than in the trunk; pattern 1 reflects this. (2) Melanoblasts are activated to proliferate synchronously upon entering into the epidermis; pattern 2 correlates with this process. (3) c-kit functions as a survival signal for proliferating melanoblasts in the epidermis. (4) The melanoblasts that enter developing hair follicles can survive without a c-kit signal; pattern 3 essentially represents the hair follicles colonized by these cells. Analysis of the melanoblast distribution of ls/ls embryos that bear a loss-of-function mutation in the endothelin 3 gene suggested that endothelin 3 is required for early melanoblast differentiation before entering into the epidermis, whereas

proliferation in the epidermis takes place without this molecule. Based on these data, we propose 4 distinct steps of embryonic melanocyte differentiation: (1) migration in the dermis, which requires both c-kit and endothelin 3; (2) a state before epidermal entry that is resistant to anti-c-kit mAb; (3) cell proliferation after entering the epidermal layer, which requires c-kit and endothelin receptor B but not endothelin 3 and (4) integration into developing hair follicles, which renders melanoblasts resistant to anti-c-kit mAb. Thus, melanoblast differentiation proceeds by alternately repeating c-kit -dependent and c-kit-independent stages and c-kit functions as a survival factor for the proliferating melanoblasts.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Antibodies, Monoclonal: AD, administration & dosage
Cell Differentiation
Cell Division
Cell Movement
Endothelins: PH, physiology
Epidermis: CH, chemistry
Epidermis: EM, embryology
Fetal Development
Hair Follicle: CY, cytology
***Hair Follicle: EM, embryology**
Isomerases: AN, analysis
***Melanocytes: CY, cytology**
Mice
Mice, Inbred Strains
Mice, Mutant Strains
Pregnancy
***Proto-Oncogene Protein c-kit: AN, analysis**
Receptors, Endothelin: PH, physiology
***Skin Pigmentation**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 5. (Isomerases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (endothelin B receptor); 0 (Antibodies, Monoclonal); 0 (Endothelins); 0 (Receptors, Endothelin)

L42 ANSWER 62 OF 109 MEDLINE
AN 96195144 MEDLINE
DN 96195144
TI Signalling mechanisms of endothelin-induced mitogenesis and melanogenesis in human melanocytes.
AU Imokawa G; Yada Y; Kimura M
CS Institute for Fundamental Research, Kao Corporation, Tochigi, Japan.
SO BIOCHEMICAL JOURNAL, **(1996 Feb 15)** 314 (Pt 1) 305-12.
Journal code: 9YO. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199610
AB To understand the signalling mechanisms involved in the dual stimulatory effects of endothelin-1 (ET-1) on DNA synthesis and melanization in cultured human melanocytes, we analysed the biological profile of ET-1 receptor and determined the effects of ET-1 on the protein kinase C, cyclic AMP system and mitogen-activated protein kinase (MAP kinase) in comparison with their relevant stimulants. The photoaffinity labelling of ET-1 receptors with Denny-Jaff reagents revealed an ET-1 receptor with a molecular mass of 51 kDa in human melanocytes. The ET(A) receptor subtype-sensitive antagonist BQ123(50 nM) or pertussis toxin (100 ng/ml) significantly suppressed the ET-1-induced intracellular calcium mobilization, indicating the presence of pertussis toxin-sensitive G-protein-coupled ET(A) receptors. An assay of protein kinase C activity revealed that 10nM ET-1 translocated cytosolic protein kinase C to membrane-bound protein kinase C within 5 min of the start of incubation. In contrast, receptor-mediated melanocyte activation by ET-1 was accompanied by an elevated level of cyclic AMP (4-fold over control) after 10-60 min of incubation, whereas 60 min of incubation of human melanocytes with c-Kit or c-Met ligands such as stem cell factor (10 nM) or basic

fibroblast growth factor (10 nM) did not elevate the cyclic AMP level. We have also demonstrated that a specific tyrosine kinase inhibitor, tyrphostin B-42 (10 microM), inhibited the ET-1-induced growth stimulation, suggesting the involvement of the tyrosine kinase pathway in growth stimulation. Consistently, an assay of MAP kinase revealed that ET-1 caused a 10-fold activation of MAP kinase after 5 min of incubation with human melanocytes in a similar way to tyrosine kinase ligands such as stem cell factor and hepatocyte growth factor. Further, the DNA synthesis stimulated by the c-Kit ligand stem cell factor at a concentration of 1 nM was synergistically enhanced by 5 nM ET-1. These results suggest that ET-induced dual cellular events in human melanocytes are closely associated with cross-talk between the protein kinase C and A and tyrosine kinase pathways.

CT Check Tags: Human
Amino Acid Sequence
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Cholera Toxin: PD, pharmacology
Cyclic AMP: ME, metabolism
DNA: BI, biosynthesis
DNA: DE, drug effects
*Endothelins: PD, pharmacology
***Melanins: BI, biosynthesis**
Melanocytes: CY, cytology
***Melanocytes: ME, metabolism**
Molecular Sequence Data
Peptides, Cyclic: PD, pharmacology
Pertussis Toxins: PD, pharmacology
Phosphodiesterase Inhibitors: PD, pharmacology
Protein Kinase C: AI, antagonists & inhibitors
Protein Kinase C: ME, metabolism
Protein-Tyrosine Kinase: ME, metabolism
Receptors, Endothelin: AI, antagonists & inhibitors
Receptors, Endothelin: CH, chemistry
***Receptors, Endothelin: ME, metabolism**
***Signal Transduction**
Stem Cell Factor: PD, pharmacology
Thiouracil: ME, metabolism
1-Methyl-3-isobutylxanthine: PD, pharmacology

RN 136553-81-6 (BQ 123); 141-90-2 (Thiouracil); 28822-58-4 (1-Methyl-3-isobutylxanthine); 60-92-4 (Cyclic AMP); 70323-44-3 (Pertussis Toxins); 9007-49-2 (DNA); 9012-63-9 (Cholera Toxin)

CN EC 2.7.1.- (Protein Kinase C); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.10.- (extracellular signal-regulated kinase 1); EC 2.7.10.- (p42 MAP Kinase); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); 0 (endothelin A receptor); 0 (Endothelins); 0 (Melanins); 0 (Peptides, Cyclic); 0 (Phosphodiesterase Inhibitors); 0 (Receptors, Endothelin); **0 (Stem Cell Factor)**

L42 ANSWER 63 OF 109 MEDLINE
AN 96104105 MEDLINE
DN 96104105
TI Coordinated mRNA expression of c-Kit with tyrosinase and TRP-1 in melanin pigmentation of normal and malignant human melanocytes and transient activation of tyrosinase by Kit/SCF-R.
AU Luo D; Chen H; Searles G; Jimbow K
CS Faculty of Medicine, University of Alberta, Edmonton, Canada.
SO MELANOMA RESEARCH, **(1995 Oct)** 5 (5) 303-9.
Journal code: BJR. ISSN: 0960-8931.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199604
AB The proto-oncogene c-Kit encodes a membrane receptor protein with intrinsic tyrosine kinase activity. Activation of c-Kit induces cell proliferation, differentiation or migration among different cell types.

The present study provides evidence that c-Kit plays an important role in the cell differentiation rather than in cell proliferation in pigment cells. We found that normal human melanocytes and a limited number of melanoma cells, e.g. WM35, WM39 and G361 cell lines, expressed the c-Kit gene together with tyrosinase and TRP-1 genes. When exposed to alpha-melanocyte stimulating hormone, these three cell lines also showed an increased tyrosinase (dopa-oxidase) activity. By incubating these cells with 20 ng/ml of stem cell factor (SCF) which is a ligand of c-Kit receptor, we found a transient increase of tyrosinase activity 2-4 h post-incubation, indicating an early response of tyrosinase activation, either by elevating tyrosinase protein expression or by tyrosinase protein modification (e.g. phosphorylation). However, Western blot analysis using anti-tyrosinase antibody suggested that there was no change of tyrosinase protein expression between SCF-treated and non-treated cells. We therefore suggest that protein modulation of tyrosinase (e.g. phosphorylation) plays an important role in c-Kit-induced melanogenesis.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Base Sequence
Cell Differentiation: PH, physiology
Cell Line
Enzyme Activation
Gene Expression
***Melanins: BI, biosynthesis**
Melanocytes: CY, cytology
***Melanocytes: ME, metabolism**
Melanocytes: PA, pathology
Melanoma: GE, genetics
*Melanoma: ME, metabolism
Molecular Sequence Data
Monophenol Monooxygenase: BI, biosynthesis
Monophenol Monooxygenase: GE, genetics
***Monophenol Monooxygenase: ME, metabolism**
Pigmentation
*Proteins: BI, biosynthesis
Proteins: GE, genetics
***Proto-Oncogene Protein c-kit: BI, biosynthesis**
Proto-Oncogene Protein c-kit: GE, genetics
Proto-Oncogenes: GE, genetics
RNA, Messenger: BI, biosynthesis
RNA, Messenger: GE, genetics
Stem Cell Factor: PD, pharmacology
Tumor Cells, Cultured

CN EC 1.14.18.1 (Monophenol Monooxygenase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (tyrosinase-related protein); 0 (Melanins); 0 (Proteins); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L42 ANSWER 64 OF 109 MEDLINE
AN 96097245 MEDLINE
DN 96097245
TI Immunohistochemical localisation of stem cell factor (SCF) with comparison of its receptor c-Kit proto-oncogene product (c-KIT) in melanocytic tumours.
AU Takahashi H; Saitoh K; Kishi H; Parsons P G
CS Division of Dermatology, Sapporo-Kosei General Hospital, Japan.
SO VIRCHOWS ARCHIV, **(1995)** 427 (3) 283-8.
Journal code: BZD. ISSN: 0945-6317.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199603
AB In order to characterise the distribution and role of stem cell factor (SCF), a recently-reported growth factor for normal melanocytes, we carried out an immunohistochemical study on benign and malignant melanocytic tumours with a comparison with the presence of its receptor c-Kit proto-oncogene product (c-KIT). In normal skin, SCF was mainly

observed in endothelial cells of blood vessels but not frequently in basal melanocytes, whereas c-KIT was predominantly localised in tissue mast cells. In benign neoplastic melanocytes (common melanocytic naevi), localisation of SCF and c-KIT was complementary: SCF was mostly found in dermal naevus cells while c-KIT was revealed in epidermal naevus cells, although the expression of the latter antigen was not frequent. Malignant melanoma cells showed less frequent expression of these antigens than those in benign lesions. Of five cultured melanoma cell lines, SCF was observed in only one, and c-KIT was not found in any melanoma cells. No quantitative or qualitative alterations assessed by Western blot analysis were induced in the presence of phenotypic modifiers (sodium butyrate and HMBA). Present data suggest that loss of SCF expression in neoplastic melanocytes is commonly associated with malignant transformation of pigment cells rather than loss of its receptor c-KIT.

CT Check Tags: Comparative Study; Human
Immunohistochemistry
***Melanocytes: ME, metabolism**
*Melanoma: ME, metabolism
Melanoma: PA, pathology
*Nevus, Pigmented: ME, metabolism
Nevus, Pigmented: PA, pathology
***Proto-Oncogene Protein c-kit: AN, analysis**
***Skin Neoplasms: ME, metabolism**
***Stem Cell Factor: AN, analysis**
Tumor Cells, Cultured: ME, metabolism

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit); 0 (Stem Cell Factor)**

L42 ANSWER 65 OF 109 MEDLINE
AN 96068655 MEDLINE
DN 96068655
TI Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder.
AU Nagata H; Worobec A S; Oh C K; Chowdhury B A; Tannenbaum S; Suzuki Y; Metcalfe D D
CS Allergic Diseases Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1995 Nov 7)** 92 (23) 10560-4.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199602
AB Both stem cells and mast cells express c-kit and proliferate after exposure to c-kit ligand. Mutations in c-kit may enhance or interfere with the ability of c-kit receptor to initiate the intracellular pathways resulting in cell proliferation. These observations suggested to us that mastocytosis might in some patients result from mutations in c-kit. cDNA synthesized from peripheral blood mononuclear cells of patients with indolent mastocytosis, mastocytosis with an associated hematologic disorder, aggressive mastocytosis, solitary mastocytoma, and chronic myelomonocytic leukemia unassociated with mastocytosis was thus screened for a mutation of c-kit. This analysis revealed that four of four mastocytosis patients with an associated hematologic disorder with predominantly myelodysplastic features had an A-->T substitution at nt 2468 of c-kit mRNA that causes an Asp-816-->Val substitution. One of one patient examined who had mastocytosis with an associated hematologic disorder had the corresponding mutation in genomic DNA. Identical or similar amino acid substitutions in mast cell lines result in ligand-independent autophosphorylation of the c-kit receptor. This mutation was not identified in the patients within the other disease categories or in 67 of 67 controls. The identification of the point mutation Asp816Val in c-kit in patients with mastocytosis with an

associated hematologic disorder provides insight not only into the pathogenesis of this form of mastocytosis but also into how hematopoiesis may become dysregulated and may serve to provide a means of confirming the diagnosis, assessing prognosis, and developing intervention strategies.

CT Check Tags: Female; Human; Male
Adolescence
Adult
Aged
Amino Acid Sequence
Base Sequence
Hematologic Diseases: CO, complications
*Hematologic Diseases: GE, genetics
Hematopoiesis: GE, genetics
*Leukocytes, Mononuclear
Mastocytosis: CO, complications
Mastocytosis: ET, etiology
***Mastocytosis: GE, genetics**
Middle Age
Molecular Sequence Data
Point Mutation
Polymorphism (Genetics)
***Proto-Oncogene Protein c-kit: GE, genetics**
*Proto-Oncogenes
RNA, Messenger: GE, genetics
Selection (Genetics)
Sequence Analysis, DNA

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (RNA, Messenger)

L42 ANSWER 66 OF 109 MEDLINE
AN 96007657 MEDLINE
DN 96007657
TI Expression of stem cell factor in cutaneous mastocytosis.
AU Hamann K; Haas N; Grabbe J; Czarnetzki B M
CS Department of Dermatology, UKRV, Freie Universitat, Berlin, Germany.
SO BRITISH JOURNAL OF DERMATOLOGY, **(1995 Aug)** 133 (2) 203-8.
Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199601
AB Stem cell factor has recently been identified as a potent growth factor for bone marrow stem cells, melanocytes and mast cells. In order to evaluate its possible role in human mastocytosis, skin lesions from 13 patients with urticaria pigmentosa and five patients with mastocytomas, and normal skin specimens from five healthy donors were studied by immunohistochemistry, using polyclonal and monoclonal (hkl-12) antibodies against stem cell factor, and a monoclonal antibody (YB5.B8) against its receptor, the c-kit proto-oncogene product. Stem cell factor expression was noted in all sections studied, with an equal distribution pattern for both antibodies, but a weaker intensity with the hkl-12 reagent. Cytoplasmic staining was noted in keratinocytes, Langerhans cells, sweat gland ductal lining cells, mast cells, endothelial cells and spindle-shaped dermal stromal cells. An intense, diffusely granular reaction pattern was noted in all cells, except for a sparse, coarsely granular pattern in mast cells and stromal cells. In urticaria pigmentosa, staining was weaker in keratinocytes, but more prominent in Langerhans cells. In all sections, toluidine blue-positive mast cells and TA 99-positive basal epidermal melanocytes were the only cells to react with the c-kit antibody. Mastocytomas and urticaria pigmentosa lesions thus exhibit different patterns of stem cell factor expression. However, a possible pathogenetic role of this factor in mastocytosis remains to be determined.

CT Check Tags: Human; Support, Non-U.S. Gov't
Adolescence
Adult

Aged
*Cell Adhesion Molecules: AN, analysis
Child
Child, Preschool
Immunohistochemistry
Infant
Keratinocytes: CH, chemistry
Langerhans Cells: CH, chemistry
Middle Age
Proto-Oncogene Protein c-kit: AN, analysis
***Stem Cell Factor: AN, analysis**
***Urticaria Pigmentosa: ME, metabolism**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Cell Adhesion Molecules); **0 (Stem Cell Factor)**

L42 ANSWER 67 OF 109 MEDLINE
AN 95403740 MEDLINE
DN 95403740
TI Human recombinant stem-cell factor induces melanocytic hyperplasia in susceptible patients.
AU Grichnik J M; Crawford J; Jimenez F; Kurtzberg J; Buchanan M; Blackwell S; Clark R E; Hitchcock M G
CS Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA..
SO JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, **(1995 Oct)** 33 (4) 577-83.
Journal code: HVG. ISSN: 0190-9622.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
AB BACKGROUND: Recombinant human stem-cell factor (SCF), a cytokine acting on hematopoietic progenitor cells, has potential for the treatment of several hematologic and oncologic disorders. In a hematology-oncology phase I trial of SCF, several patients had cutaneous **hyperpigmentation** at the SCF subcutaneous injection sites. OBJECTIVE: Our purpose was to investigate the pathogenesis of this **hyperpigmentation** phenomenon. METHODS: Skin biopsy specimens were obtained before, at the completion of, and after SCF therapy and were processed for histology, immunohistology, and electron microscopy. RESULTS: Skin at the site of SCF injection had an increased number of melanocytes, increased melanocytic dendrite extension, and melanin as compared with noninjected tissue. Immunohistochemical stains revealed an increase in staining with melanocyte-specific monoclonal antibodies HMB-45 and NKI/beteb, and a monoclonal antibody to the receptor for SCF, c-kit. CONCLUSION: Subcutaneous injection of SCF results in hyperplasia of melanocytes. SCF may be useful in the treatment of melanocytopenic disorders, but caution may be necessary in patients with disorders of melanocyte proliferation.
CT Check Tags: Comparative Study; Support, Non-U.S. Gov't
Antibodies, Monoclonal
Antineoplastic Agents, Combined: TU, therapeutic use
Carboplatin: AD, administration & dosage
Carcinoma, Non-Small-Cell Lung: DT, drug therapy
Cell Adhesion Molecules: AD, administration & dosage
*Cell Adhesion Molecules: AE, adverse effects
Dendrites: DE, drug effects
Dendrites: PA, pathology
Dendrites: UL, ultrastructure
Disease Susceptibility
Etoposide: AD, administration & dosage
Follow-Up Studies
Hematopoietic Cell Growth Factors: AD, administration & dosage
*Hematopoietic Cell Growth Factors: AE, adverse effects

***Hyperpigmentation: CI, chemically induced**
Hyperpigmentation: PA, pathology
Hyperplasia
Injections, Subcutaneous
Lung Neoplasms: DT, drug therapy
Melanins: AN, analysis
Melanocytes: DE, drug effects
Melanocytes: PA, pathology
Melanocytes: UL, ultrastructure
Recombinant Proteins
RN 33419-42-0 (Etoposide); 41575-94-4 (Carboplatin)
CN 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents, Combined); 0 (Cell Adhesion Molecules); 0 (Hematopoietic Cell Growth Factors); 0 (Melanins); 0 (Recombinant Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 68 OF 109 MEDLINE
AN 95395283 MEDLINE
DN 95395283
TI Effects of monoclonal anti-c-kit antibody (ACK2) on melanocytes in newborn mice.
AU Okura M; Maeda H; Nishikawa S; Mizoguchi M
CS Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan.
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1995 Sep)** 105 (3) 322-8.
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199512
AB Previous studies indicate that c-Kit is required for postnatal melanocyte development. To understand the precise mechanisms of c-Kit dependence, we studied melanocyte development in newborn C57BL/6 mice by means of peritoneal injection of a monoclonal anti-c-Kit antibody (ACK2), which blocks c-Kit functions. The mice were injected once or more with ACK2 at various intervals after birth. In experiment 1, skin samples were examined on day 10 post-partum and in experiment 2 they were examined daily until day 10 post-partum. We studied melanocytes in the hair follicles, epidermis, and dermis by light and electron microscopy with dopa reactions and immunohistochemistry. Epidermal melanocytes in untreated mice were dopa negative and c-Kit positive on day 0 post-partum but became dopa positive soon thereafter. In ACK2-treated mice, the earlier the mice received ACK2 injections after birth, the fewer melanocytes they had, not only in the epidermis, but also in follicles. In these mice, melanocytes that had undergone apoptosis in the dermis and the follicles were detected ultrastructurally. Some appeared to have produced tyrosinase, because they had dopa-positive melanosomes. These results suggest that melanocytes in newborn mice are c-Kit dependent and undergo apoptosis when c-Kit receptors are blocked by ACK2 in the early days after birth. During this c-Kit-dependent period, melanocytes differentiate from dopa negative to positive and migrate from the epidermis to hair follicles.
CT Check Tags: Animal
Animals, Newborn
*Antibodies, Monoclonal: IM, immunology
*Antibodies, Monoclonal: PD, pharmacology
Apoptosis
Dopa: ME, metabolism
Epidermis: CY, cytology
Hair: CY, cytology
Hair: GD, growth & development
Hair: ME, metabolism
Hair Color: DE, drug effects
***Melanocytes: DE, drug effects**
Melanocytes: ME, metabolism
Melanocytes: UL, ultrastructure
Mice

Mice, Inbred C57BL
Microscopy, Electron
*Proto-Oncogene Proteins: IM, immunology
***Receptor Protein-Tyrosine Kinases: IM, immunology**
***Receptors, Colony-Stimulating Factor: IM, immunology**
RN 63-84-3 (Dopa)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Antibodies, Monoclonal); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)

L42 ANSWER 69 OF 109 MEDLINE
AN 95391554 MEDLINE
DN 95391554
TI Human piebaldism: relationship between phenotype and site of kit gene mutation.
AU Ward K A; Moss C; Sanders D S
CS Department of Dermatology, General Hospital, Birmingham, U.K.
SO BRITISH JOURNAL OF DERMATOLOGY, **(1995 Jun)** 132 (6) 929-35.
Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
AB Human piebaldism is a rare autosomal dominant disorder characterized by congenital depigmented patches of skin and hair. Piebaldism results from mutations of the kit proto-oncogene, which encodes a cell-surface receptor, tyrosine kinase, whose ligand is the stem/mast cell growth factor. We report four unrelated patients with piebaldism and consider the variations in phenotype in relation to the site of the kit gene mutation.
CT Check Tags: Case Report; Female; Human; Male
Adolescence
Adult
DNA Mutational Analysis
*Genes, Dominant
Mast Cells
Mutation
Pedigree
Phenotype
***Piebaldism: GE, genetics**
Piebaldism: PA, pathology
*Proto-Oncogene Proteins: GE, genetics
***Receptor Protein-Tyrosine Kinases: GE, genetics**
***Receptors, Colony-Stimulating Factor: GE, genetics**
Skin: PA, pathology
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)
GEN kit

L42 ANSWER 70 OF 109 MEDLINE
AN 95375307 MEDLINE
DN 95375307
TI Steel and c-kit in the development of avian melanocytes: a study of normally pigmented birds and of the **hyperpigmented** mutant silky fowl.
AU Lecoin L; Lahav R; Martin F H; Teillet M A; Le Douarin N M
CS Institut d'Embryologie Cellulaire et Moleculaire du CNRS, Nogent-sur-Marne, France.
SO DEVELOPMENTAL DYNAMICS, **(1995 May)** 203 (1) 106-18.
Journal code: A9U. ISSN: 1058-8388.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512

AB We describe here the expression of c-kit and Steel (Sl) genes during the development of melanocytes in normally pigmented strains of chick and quail compared to unpigmented (White Leghorn) and **hyperpigmented** (Silky Fowl) strains of chickens. By using the quail/chick chimera system, we found that the neural crest cells, which migrate dorso-laterally in the subectodermal mesenchyme to give rise to the melanocytes, express c-kit as early as E4, that is about 2 days after they have left the neural primordium. The Sl gene is expressed from E4 onward in the epidermis but not at all in the dermis at any developmental stage. As feather buds develop, Sl mRNA becomes restricted to the apical region of the feather filaments. During formation of the barbs and barbules of the down feather, production of the Steel factor is restricted to the external epidermal cells of the barbules. The cell bodies of the c-kit-positive melanocytes are then located in the internal border of the epidermal ridges and extend their processes toward the source of the Steel factor. We propose that the spatial restriction of Sl gene activity at that stage accounts for the morphology of the melanocytes and their vectorial secretion of melanin to the external barbule cells. As a whole, these results show that during skin development c-kit positive cells are present in the Steel factor-producing areas at the time when melanoblasts proliferate and differentiate. Interestingly, in the mouse, previous studies showed that the Sl gene is activated in the dermis where melanoblasts undergo most of their expansion (Nishikawa et al. [1991] EMBO J. 10:2111-2118). In the unpigmented and **hyperpigmented** mutants that we studied, expression of the Sl message, as judged quantitatively in Northern blots (for the SF embryos) or spatially by in situ hybridization, is similar to that observed in normal birds. In SF embryos the c-kit expressing melanoblasts migrate initially in the dorso-lateral migration pathway as in normal birds. However their number increases considerably in the dermis from E5 onward. From E7, they invade mesodermally derived organs that do not express the Sl gene. This suggests that another, still unknown, factor(s) is responsible for the survival, the proliferation, and the extensive spreading of melanocytic cells within the mesoderm of this mutant.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Movement
Chick Embryo
Chimera: GE, genetics
Feathers: EM, embryology
Feathers: ME, metabolism
Gene Expression Regulation, Developmental
*Hematopoietic Cell Growth Factors: GE, genetics
In Situ Hybridization
Melanocytes: CY, cytology
***Melanocytes: ME, metabolism**
Mutation
Neural Crest: CY, cytology
Neural Crest: ME, metabolism
Pigmentation Disorders: GE, genetics
*Proto-Oncogene Proteins: GE, genetics
Quail
***Receptor Protein-Tyrosine Kinases: GE, genetics**
***Receptors, Colony-Stimulating Factor: GE, genetics**
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
***Skin Pigmentation: GE, genetics**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

GEN Sl; c-kit

L42 ANSWER 71 OF 109 MEDLINE
AN 95315064 MEDLINE
DN 95315064
TI Identification of p90RSK as the probable CREB-Ser133 kinase in human

melanocytes.
AU Bohm M; Moellmann G; Cheng E; Alvarez-Franco M; Wagner S; Sassone-Corsi P; Halaban R
CS Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut 06520-8059, USA.
NC CA44542 (NCI)
AR39848 (NIAMS)
AR41942 (NIAMS)
SO CELL GROWTH AND DIFFERENTIATION, **(1995 Mar)** 6 (3) 291-302.
Journal code: AYH. ISSN: 1044-9523.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
AB Normal human melanocytes proliferate in vitro only in response to costimulation by at least two selected peptide growth factors. In the presence of only one mitogen, melanocytes become quiescent or die. These mitogens also enhance expression of differentiated functions, since in their presence the proliferating melanocytes become progressively more pigmented. To assess the intermediates participating in this dual response, we have determined the activated state of several known ligand-induced signal transducers. We demonstrate that hepatocyte growth factor/scatter factor, mast/stem-cell growth factor, basic fibroblast growth factor, and endothelin-1 induce phosphorylation of Ser133 within the KID domain of the cAMP-responsive element binding protein, a modification necessary for transcriptional activation of all members of this family of transcription factors, including also cAMP-responsive element modulator tau and activating transcription factor 1. The costimulation with synergistic growth factors prolonged the phosphorylated state and activity of the mitogen-activated protein kinase 2 cascade. cAMP-responsive element binding protein Ser133 phosphorylation in response to synergistic growth factors was due probably to the activation of p90RSK and, to a lesser extent, to p70S6K. Our findings support the concept that signals initiated at the cell surface converge on regulatory proteins that sustain both cell division and differentiation.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Count
Cell Division
Cells, Cultured
Cyclic AMP: ME, metabolism
Drug Synergism
*DNA-Binding Protein, Cyclic AMP-Responsive: ME, metabolism
Endothelins: PD, pharmacology
Fibroblast Growth Factor, Basic: PD, pharmacology
*Growth Substances: PD, pharmacology
Hematopoietic Cell Growth Factors: PD, pharmacology
Hepatocyte Growth Factor: PD, pharmacology
Infant, Newborn
Melanocytes: CY, cytology
***Melanocytes: ME, metabolism**
Phosphorylation
***Protein-Serine-Threonine Kinases: ME, metabolism**
Recombinant Fusion Proteins: BI, biosynthesis
*Serine: ME, metabolism
Time Factors
Transcription Factors: ME, metabolism
RN 56-45-1 (Serine); 60-92-4 (Cyclic AMP); 67256-21-7 (Hepatocyte Growth Factor)
CN EC 2.7.10 (Protein-Serine-Threonine Kinases); EC 2.7.10.- (Ribosomal Protein S6 Kinase); 0 (DNA-Binding Protein, Cyclic AMP-Responsive); 0 (Endothelins); 0 (Fibroblast Growth Factor, Basic); 0 (Growth Substances); 0 (Hematopoietic Cell Growth Factors); 0 (Recombinant Fusion Proteins); **0 (Stem Cell Factor)**; 0 (Transcription Factors)

L42 ANSWER 72 OF 109 MEDLINE

AN 95309135 MEDLINE
DN 95309135
TI A cloned, immortal line of murine melanoblasts inducible to differentiate to melanocytes.
AU Sviderskaya E V; Wakeling W F; Bennett D C
CS St George's Hospital Medical School, London, UK..
SO DEVELOPMENT, **(1995 May)** 121 (5) 1547-57.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199509
AB Cultures of differentiated melanocytes can readily be grown from the dissociated epidermis of neonatal mice, and immortal cell lines often develop from these. However, the first cells that grow and transiently dominate the cultures, while similar to melanocytes, are unpigmented. These have been shown to be precursors of melanocytes and may be termed melanoblasts. Under our previous standard culture conditions, involving the use of keratinocyte feeder cells, foetal calf serum, the phorbol ester 12-O-tetradecanoyl phorbol acetate (TPA) and cholera toxin, all the melanoblasts spontaneously differentiated to pigmented melanocytes within about 3 weeks. We now describe some factors affecting the proliferation and differentiation of diploid murine melanoblasts in the presence of serum. Murine stem cell factor/steel factor (SCF), basic fibroblast growth factor (bFGF) and murine leukaemia inhibitory factor/differentiation-inhibiting activity (LIF/DIA) all increased melanoblast numbers. SCF and LIF also slightly inhibited melanoblast differentiation, while cholera toxin and TPA promoted differentiation. Using some of these findings, and by regular replacement of keratinocyte or fibroblastoid feeder cells, we have established a clonal line of immortal murine melanoblasts, 'melb-a'. These cells express tyrosinase-related protein-2 but not, in general, tyrosinase. They can be induced to differentiate irreversibly to functional melanocytes (also proliferative and immortal) by plating in the absence of feeder cells. Thus a new immortal melanocyte line, 'melan-a2', has also been produced.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Adhesion Molecules: PD, pharmacology
Cell Count
Cell Differentiation: DE, drug effects
Cell Division
*Cell Line
Cholera Toxin: PD, pharmacology
Clone Cells
***Epidermis: CY, cytology**
Epidermis: EN, enzymology
Fibroblast Growth Factor, Basic: PD, pharmacology
Growth Inhibitors: PD, pharmacology
Hematopoietic Cell Growth Factors: PD, pharmacology
Histocytochemistry
Immunohistochemistry
Isomerases: ME, metabolism
Lymphokines: PD, pharmacology
***Melanocytes: CY, cytology**
Melanocytes: EN, enzymology
Mice
Mice, Inbred C57BL
Tetradecanoylphorbol Acetate: PD, pharmacology
RN 16561-29-8 (Tetradecanoylphorbol Acetate); 9012-63-9 (Cholera Toxin)
CN EC 5. (Isomerases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (Cell Adhesion Molecules); 0 (D factor); 0 (Fibroblast Growth Factor, Basic); 0 (Growth Inhibitors); 0 (Hematopoietic Cell Growth Factors); 0 (Lymphokines); **0 (Stem Cell Factor)**

L42 ANSWER 73 OF 109 MEDLINE
AN 95301099 MEDLINE

DN 95301099
TI Steel factor directs melanocyte development in vitro through selective regulation of the number of c-kit+ progenitors.
AU Reid K; Nishikawa S; Bartlett P F; Murphy M
CS Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, Victoria, Australia.
SO DEVELOPMENTAL BIOLOGY, **(1995 Jun)** 169 (2) 568-79.
Journal code: E7T. ISSN: 0012-1606.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199509
AB Studies of mice containing mutations in the genes for a receptor tyrosine kinase, c-kit, or its cognate ligand, Steel factor (SLF), establish that this signaling pathway is required for the development of melanocytes from their precursors in the embryonic neural crest (NC). In order to define the mechanism of this requirement, we have labeled cells expressing c-kit with an anti-c-kit antibody (ACK2) and studied the action of SLF on these cells in cultures of murine trunk NC. c-kit positive (c-kit+) cells first appeared after 2 days in culture and were morphologically indistinguishable from other NC cells. These cells subsequently expressed tyrosinase-related protein, an early marker for the melanocyte lineage, and became pigmented in the presence of a phorbol ester. Further, elimination of the c-kit+ population, by incubating the cultures in ACK2, resulted in the ablation of the melanocyte population, but had no effect on the generation of other neural crest derivatives. These data indicate that c-kit+ cells arising from the neural crest are melanocyte progenitors. The addition of SLF to these cultures stimulated an increase in the number of c-kit+ cells, and further studies indicated that SLF acts as both a survival and a proliferative factor for c-kit+ cells. These findings provide a mechanism of regulation of melanocyte development, whereby c-kit is exclusively expressed by melanocyte progenitors within the neural crest precursor population, and subsequent survival and proliferation of these progenitors is regulated by SLF.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Division
Cell Survival
Cells, Cultured
*Hematopoietic Cell Growth Factors: ME, metabolism
***Melanocytes: CY, cytology**
Melanocytes: ME, metabolism
Mice
Mice, Inbred CBA
Neural Crest: CY, cytology
Neural Crest: ME, metabolism
Pigmentation
*Proto-Oncogene Proteins: ME, metabolism
***Receptor Protein-Tyrosine Kinases: ME, metabolism**
***Receptors, Colony-Stimulating Factor: ME, metabolism**
Schwann Cells: ME, metabolism
***Stem Cells: CY, cytology**
Stem Cells: ME, metabolism
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); **0 (Stem Cell Factor)**

L42 ANSWER 74 OF 109 MEDLINE
AN 95282669 MEDLINE
DN 95282669
TI Genetic disorders of pigmentation.
AU Spritz R A; Hearing V J Jr
CS Department of Medical Genetics, University of Wisconsin, Madison 53706, USA.
SO ADVANCES IN HUMAN GENETICS, **(1994)** 22 1-45. Ref: 209

Journal code: 2N6. ISSN: 0065-275X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199509
CT Check Tags: Animal; Human
Albinism: GE, genetics
Amino Acid Sequence
Base Sequence
Mammals
Melanocytes: PH, physiology
Mice
Monophenol Monooxygenase: GE, genetics
***Pigmentation Disorders: GE, genetics**
Point Mutation
Polymorphism (Genetics)
Proto-Oncogene Proteins: GE, genetics
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptors, Colony-Stimulating Factor: GE, genetics
Skin: ME, metabolism
Skin: PA, pathology
CN EC 1.14.18.1 (Monophenol Monooxygenase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)
GEN KIT; TYR

L42 ANSWER 75 OF 109 MEDLINE
AN 95237006 MEDLINE
DN 95237006
TI Soluble and cell-bound forms of steel factor activity play distinct roles in melanocyte precursor dispersal and survival on the lateral neural crest migration pathway.
AU Wehrle-Haller B; Weston J A
CS Institute of Neuroscience, University of Oregon, Eugene 97403.
NC DE-04316 (NIDCR)
DE-05620 (NIDCR)
SO DEVELOPMENT, **(1995 Mar)** 121 (3) 731-42.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199507
AB Trunk neural crest cells segregate from the neuroepithelium and enter a 'migration staging area' lateral to the embryonic neural tube. After some crest cells in the migration staging area have begun to migrate on a medial pathway, a subpopulation of crest-derived cells remaining in the migration staging area expresses mRNAs for the receptor tyrosine kinase, c-kit, and tyrosinase-related protein-2, both of which are characteristic of melanocyte precursors. These putative melanocyte precursors are subsequently observed on the lateral crest migration pathway between the dermatome and overlying epithelium, and then dispersed in nascent dermal mesenchyme. Melanocyte precursors transiently require the c-kit ligand, Steel factor for survival. Although Steel factor mRNA is transiently expressed in the dorsal dermatome before the onset of trunk neural crest cell dispersal on the lateral pathway, it is no longer produced by dermatomal cells when melanocyte precursors have dispersed in the dermal mesenchyme. To assess the role of Steel factor in migration of melanocyte precursors on the lateral pathway, we analyzed melanocyte precursor dispersal and fate on the lateral pathway of two different Sl mutants, Sl, a null allele, and Sld, which lacks cell surface-associated Steel factor but produces a soluble form. No melanocyte precursors were detected in the dermatome of embryos homozygous for the Sl allele or in W mutants that

lack functional c-kit. In contrast, in embryos homozygous for the Sld allele, melanocyte precursors appeared on the lateral pathway, but subsequently disappear from the dermis. These results suggest that soluble Steel factor is required for melanocyte precursor dispersal on the lateral pathway, or for their initial survival in the migration staging area. In contrast, membrane-bound Steel factor appears to promote melanocyte precursor survival in the dermis.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Movement: PH, physiology
Cell Survival: PH, physiology
*Central Nervous System: EM, embryology
Gene Expression
Genotype
Hematopoietic Cell Growth Factors: GE, genetics
*Hematopoietic Cell Growth Factors: PH, physiology
Immunohistochemistry
In Situ Hybridization
***Melanocytes: CY, cytology**
*Mesoderm: CY, cytology
Mesoderm: PH, physiology
Mice
Mice, Mutant Strains
Molecular Sequence Data
Proto-Oncogene Proteins: GE, genetics
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptors, Colony-Stimulating Factor: GE, genetics
RNA, Messenger: AN, analysis
***Skin: EM, embryology**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

GEN SL; c-kit

L42 ANSWER 76 OF 109 MEDLINE
AN 95196972 MEDLINE
DN 95196972
TI Effect of the Steel gene product on melanogenesis in avian neural crest cell cultures.
AU Lahav R; Lecoin L; Ziller C; Nataf V; Carnahan J F; Martin F H; Le Douarin N M
CS Institut d'Embryologie Cellulaire et Moleculaire, Centre National de la Recherche Scientifique et du Coll`ege de France, Nogent-sur-Marne.
SO DIFFERENTIATION, **(1994 Dec)** 58 (2) 133-9.
Journal code: E99. ISSN: 0301-4681.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199506
AB Mutations at the Steel (Sl) and dominant white spotting (W) loci affect three embryonic lineages: primordial germ cells, hemopoietic stem cells and neural-crest-derived melanocytes. The gene products of these loci are a peptide growth factor, called here stem cell factor (SCF), and its tyrosine kinase receptor, the proto-oncogene c-kit. We have studied how chicken recombinant SCF affects the development of melanocytes from quail neural crest cells in secondary culture under defined conditions. We observed that the total number of neural crest cells, of melanocytes and of their precursors was higher in the presence than in the absence of SCF. Labelling with bromodeoxyuridine showed that SCF had a modest and transient mitogenic effect on the neural crest population. SCF also enhanced the differentiation rate of melanocyte precursors, recognized by the "melanocyte early marker" monoclonal antibody (MelEM MAb), and of melanocytes, since the proportion of both subpopulations significantly increased in the presence of SCF. Finally, SCF increased the survival of the neural crest population since in its presence the total number of

cells remained stable while it gradually declined in control cultures. Our results support the notion that SCF sustains the survival of the neural crest population and stimulates the rate of the melanogenic differentiation process.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Differentiation: PH, physiology
Cell Division: PH, physiology
Cell Survival: PH, physiology
Cells, Cultured
*Hematopoietic Cell Growth Factors: PH, physiology
***Melanocytes: PH, physiology**
*Neural Crest: CY, cytology
Proto-Oncogene Proteins: PH, physiology
*Quail: EM, embryology
Receptor Protein-Tyrosine Kinases: PH, physiology
Receptors, Colony-Stimulating Factor: PH, physiology

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); **0 (Stem Cell Factor)**

GEN S1

L42 ANSWER 77 OF 109 MEDLINE

AN 95194867 MEDLINE

DN 95194867

TI Expression of the c-kit receptor in hypomelanosis: a comparative study between piebaldism, naevus depigmentosus and vitiligo.

AU Dippel E; Haas N; Grabbe J; Schadendorf D; Hamann K; Czarnetzki B M

CS Department of Dermatology, University Hospital R. Virchow, Freie Universitat Berlin, Germany.

SO BRITISH JOURNAL OF DERMATOLOGY, **(1995 Feb)** 132 (2) 182-9. Journal code: AW0. ISSN: 0007-0963.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199506

AB In order to investigate possible alterations in c-kit protein expression on epidermal melanocytes in different hypopigmentary disorders, we have examined skin specimens from one patient with piebaldism, one patient with naevus depigmentosus, and five patients with vitiligo. Cryosections were examined by immunohistochemistry using monoclonal antibodies against the c-kit protein (YB5.B8) and melanosomes (TA99). In piebaldism, hypomelanotic epidermis contained only a few TA99-positive epidermal melanocytes and no detectable c-kit protein, whereas in naevus depigmentosus the expression of c-kit protein was strong, and TA99 immunoreactivity was faint. In vitiligo lesions, no epidermal immunoreactivity for melanosomes or c-kit protein was found. Normally pigmented skin of all patients showed immunoreactivity of epidermal melanocytes for both c-kit protein and melanosomes. Different hypomelanotic lesions can thus be differentiated by absent melanocyte c-kit protein and low or no expression of melanosomal marker in piebaldism, normal c-kit but low melanosome expression in naevus depigmentosus, and the absence of all melanocyte markers in vitiligo.

CT Check Tags: Comparative Study; Female; Human; Male
Adult
Aged
Cell Count
Gene Expression
***Hypopigmentation: GE, genetics**
Hypopigmentation: PA, pathology
Immunohistochemistry
Melanocytes: ME, metabolism
Middle Age
Nevus: GE, genetics
Nevus: ME, metabolism

Piebaldism: GE, genetics
Piebaldism: ME, metabolism
*Proto-Oncogene Proteins: BI, biosynthesis
***Receptor Protein-Tyrosine Kinases: BI, biosynthesis**
***Receptors, Colony-Stimulating Factor: BI, biosynthesis**
Skin Neoplasms: GE, genetics
Skin Neoplasms: ME, metabolism
Vitiligo: GE, genetics
Vitiligo: ME, metabolism
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)
GEN c-kit

L42 ANSWER 78 OF 109 MEDLINE
AN 95126141 MEDLINE
DN 95126141
TI Novel mutations and deletions of the KIT (steel factor receptor) gene in human piebaldism.
AU Ezoe K; Holmes S A; Ho L; Bennett C P; Bolognia J L; Brueton L; Burn J; Falabella R; Gatto E M; Ishii N; et al
CS Department of Medical Genetics, University of Wisconsin, Madison 53706.
NC AR 39892 (NIAMS)
SO AMERICAN JOURNAL OF HUMAN GENETICS, **(1995 Jan)** 56 (1) 58-66.
Journal code: 3IM. ISSN: 0002-9297.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199504
AB Piebaldism is an autosomal dominant genetic disorder of pigmentation characterized by white patches of skin and hair. Melanocytes are lacking in these hypopigmented regions, the result of mutations of the KIT gene, which encodes the cell surface receptor for steel factor (SLF). We describe the analysis of 26 unrelated patients with piebaldism-like hypopigmentation--17 typical patients, 5 with atypical clinical features or family histories, and 4 with other disorders that involve white spotting. We identified novel pathologic mutations or deletions of the KIT gene in 10 (59%) of the typical patients, and in 2 (40%) of the atypical patients. Overall, we have identified pathologic KIT gene mutations in 21 (75%) of 28 unrelated patients with typical piebaldism we have studied. Of the patients without apparent KIT mutations, none have apparent abnormalities of the gene encoding SLF itself (MGF), and genetic linkage analyses in two of these families are suggestive of linkage of the piebald phenotype to KIT. Thus, most patients with typical piebaldism appear to have abnormalities of the KIT gene.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adolescence
Adult
Amino Acid Sequence
Base Sequence
Blotting, Southern
Child
Child, Preschool
DNA Mutational Analysis
Genes, Dominant
Genes, Structural
Hematopoietic Cell Growth Factors: DF, deficiency
Hematopoietic Cell Growth Factors: GE, genetics
Lod Score
Molecular Sequence Data
*Mutation
***Piebaldism: GE, genetics**
Proto-Oncogene Proteins: DF, deficiency
*Proto-Oncogene Proteins: GE, genetics

Receptor Protein-Tyrosine Kinases: DF, deficiency
***Receptor Protein-Tyrosine Kinases: GE, genetics**
Receptors, Colony-Stimulating Factor: DF, deficiency
***Receptors, Colony-Stimulating Factor: GE, genetics**
Sequence Deletion
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); **0 (Stem Cell Factor)**
GEN KIT; MGF

L42 ANSWER 79 OF 109 MEDLINE
AN 95052798 MEDLINE
DN 95052798
TI Molecular basis of human piebaldism.
AU Spritz R A
CS Department of Medical Genetics, University of Wisconsin, Madison 53706.
NC AR39892 (NIAMS)
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, **(1994 Nov)** 103 (5 Suppl) 137S-140S. Ref: 40
Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199502
AB Piebaldism is an autosomal dominant genetic disorder of pigmentation characterized by congenital patches of white skin and hair that lack melanocytes. Piebaldism results from mutations of the KIT proto-oncogene, which encodes the cell-surface receptor transmembrane tyrosine kinase for an embryonic growth factor, Steel factor. Several pathologic mutations of the KIT gene have now been identified in different patients with piebaldism. Correlation of these mutations with the associated piebald phenotypes has led to the recognition of a hierarchy of three classes of mutations that result in a graded series of piebald phenotypes, and to improved understanding of the mechanisms that underlie dominant genetic disorders.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Genes
Mutation
Phenotype
Piebaldism: CL, classification
***Piebaldism: GE, genetics**
Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins: ME, metabolism
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptor Protein-Tyrosine Kinases: ME, metabolism
Receptors, Colony-Stimulating Factor: GE, genetics
Receptors, Colony-Stimulating Factor: ME, metabolism
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)

L42 ANSWER 80 OF 109 MEDLINE
AN 95002968 MEDLINE
DN 95002968
TI Mast cells cultured from the peripheral blood of normal donors and patients with mastocytosis originate from a CD34+/Fc epsilon RI- cell population.
AU Rottem M; Okada T; Goff J P; Metcalfe D D
CS Allergic Diseases Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.
SO BLOOD, **(1994 Oct 15)** 84 (8) 2489-96.
Journal code: A8G. ISSN: 0006-4971.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199501
AB Mast cells may be cultured from human peripheral blood in the presence of recombinant human stem cell factor (rhSCF). The characteristics of the cells in peripheral blood that give rise to mast cells are unknown. Because mast cell precursors in human marrow are CD34+, human peripheral blood mononuclear cells from patients with mastocytosis and normal controls were sorted on the basis of CD34 expression and the positive and negative cell populations were cultured in rhSCF, recombinant human interleukin-3 (rhIL-3), or both for 6 weeks. Cell cultures were examined every 2 weeks for total and mast cell number and cell differential using Wright Giemsa and acid toluidine blue stains and antibodies to mast cell tryptase and chymase, cell-associated histamine, and expression of CD34, c-kit, Fc epsilon RI, and Fc gamma RII using flow cytometric analysis. The ultrastructural anatomy of mast cells was examined by electron microscopy. Peripheral blood CD34+ cells cultured in rhSCF with or without rhIL-3 gave rise to cell cultures consisting of greater than 80% mast cells by 6 weeks. CD34+ cells cultured in rhIL-3 alone did not give rise to mast cells, whereas rhIL-3 plus rhSCF increased the final mast cell number eightfold when compared with cells cultured in rhSCF alone. Mast cells increased concomitantly with a decrease in large undifferentiated mononuclear cells. CD34- cells did not give rise to mast cells. Histamine content per cell at 6 weeks was approximately 5 pg. Electron microscopy of 4-week cultures showed immature mast cells containing predominantly tryptase-positive granules that were either homogeneous or contained lattice structures, partial scroll patterns, or central dense cores and mixtures of vesicles, fine granular material, and particles. The CD34+ population at day 0 expressed Kit (65%) and Fc gamma RII (95%), but not Fc epsilon RI, by fluorescence-activated cell sorter analysis. At 6 weeks, CD34+-derived mast cells exhibited Fc epsilon RI in addition to Kit and Fc gamma RII, and were negative for CD34 antigen. Patients with mastocytosis showed a higher number of mast cells per CD34+ cell cultured compared with normal controls. Thus, the mast cell precursor in human peripheral blood is CD34+/Fc epsilon RI- and gives rise to mast cells in the presence of rhSCF with or without rhIL-3, and the number of mast cells arising per CD34+ cell in culture is greater when the CD34+ cells are obtained from patients with mastocytosis compared with normal subjects.
CT Check Tags: Human
*Antigens, CD: AN, analysis
Cell Differentiation
Cell Separation
Cells, Cultured
Cytoplasmic Granules: EN, enzymology
Cytoplasmic Granules: UL, ultrastructure
Flow Cytometry
Hematopoietic Cell Growth Factors: PD, pharmacology
Histamine: AN, analysis
Interleukin-3: PD, pharmacology
Kinetics
Lymphocyte Count
*Mast Cells: CY, cytology
Mast Cells: IM, immunology
***Mastocytosis: PA, pathology**
Microscopy, Electron
Proto-Oncogene Proteins: AN, analysis
Receptor Protein-Tyrosine Kinases: AN, analysis
Receptors, Colony-Stimulating Factor: AN, analysis
***Receptors, IgE: AN, analysis**
Recombinant Proteins: PD, pharmacology
Serine Endopeptidases: AN, analysis
RN 51-45-6 (Histamine)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); EC 3.4.21 (Serine Endopeptidases); EC

3.4.21.39 (chymase); EC 3.4.21.59 (tryptase); 0 (Antigens, CD); 0 (Antigens, CD34); 0 (Hematopoietic Cell Growth Factors); 0 (Interleukin-3); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); 0 (Receptors, IgE); 0 (Recombinant Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 81 OF 109 MEDLINE
AN 94357068 MEDLINE
DN 94357068
TI W-sash affects positive and negative elements controlling c-kit expression: ectopic c-kit expression at sites of kit-ligand expression affects melanogenesis.
AU Duttlinger R; Manova K; Chu T Y; Gyssler C; Zelenetz A D; Bachvarova R F; Besmer P
CS Molecular Biology Program, Sloan Kettering Institute, New York, NY.
NC R37 CA 32926 (NCI)
HD 06910 (NICHD)
SO DEVELOPMENT, **(1993 Jul)** 118 (3) 705-17.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199412
AB The receptor tyrosine kinase c-kit and its cognate ligand KL are encoded at the white spotting (W) and steel (Sl) loci of the mouse, respectively. Mutations at both the W and the Sl locus cause deficiencies in gametogenesis, melanogenesis and hematopoiesis (erythrocytes and mast cells). The W-sash mutation differs from most W mutations in that it affects primarily mast cells and melanogenesis but not other cellular targets of W and Sl mutations. Thus, Wsh/Wsh mice are fertile and not anemic, but they lack mast cells in their skin and intestine and are devoid of coat pigment. Heterozygotes are black with a broad white sash/belt in the lumbar region. In order to determine the basis for the phenotypes of W-sash mice, we investigated c-kit RNA and protein expression patterns in adult Wsh/Wsh mice and during embryonic development. We show that c-kit expression is absent in bone-marrow-derived Wsh/Wsh mast cells, the fetal and the adult lung, and the digestive tract at embryonic day 13 1/2 (E13 1/2), tissues that normally express c-kit. Unexpectedly, in E10 1/2 and 11 1/2d Wsh/Wsh embryos, we found c-kit expression in the dermatome of the somites, the mesenchyme around the otic vesicle and the floorplate of the neural tube, structures known to express the c-kit ligand in wild-type embryos. The ectopic c-kit expression in Wsh homozygous embryos does not affect c-kit ligand expression. The presumed Wsh/Wsh melanoblasts appeared to be normal and, at E10 1/2, similar numbers were found in normal and homozygous mutant embryos. At E13 1/2 +/+ embryos had a graded distribution of melanoblasts from cranial to caudal with a minimum in the lumbar region. Whereas E13 1/2 homozygous Wsh/Wsh embryos essentially lacked c-kit-positive cells in the skin, E13 1/2 heterozygous Wsh/+ embryos had reduced numbers of melanoblasts compared to +/+ with few or none in the lumbar region (future sash). It is proposed that ectopic c-kit expression in the somitic dermatome affects early melanogenesis in a dominant fashion. Molecular analysis of Wsh chromosomal DNA revealed a deletion or rearrangement in the vicinity of the c-kit gene. These results provide an explanation for the Wsh phenotype and have implications for the control of c-kit expression.
CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Cells, Cultured
DNA: AN, analysis
Gene Expression Regulation, Enzymologic
Gestational Age
Lung: ME, metabolism
Mast Cells: ME, metabolism
***Melanins: BI, biosynthesis**
Melanocytes: ME, metabolism

Mesoderm
Mice
Mice, Inbred C3H
Mice, Inbred C57BL
Mice, Mutant Strains: EM, embryology
*Mice, Mutant Strains: GE, genetics
Mice, Mutant Strains: ME, metabolism
Mutation
Pigmentation Disorders: EM, embryology
***Pigmentation Disorders: GE, genetics**
Pigmentation Disorders: ME, metabolism
*Proto-Oncogene Proteins: BI, biosynthesis
Proto-Oncogene Proteins: GE, genetics
***Receptor Protein-Tyrosine Kinases: BI, biosynthesis**
Receptor Protein-Tyrosine Kinases: GE, genetics
***Receptors, Colony-Stimulating Factor: BI, biosynthesis**
Receptors, Colony-Stimulating Factor: GE, genetics
RN 9007-49-2 (DNA)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Melanins); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)
GEN Sl; Wsh; c-kit; Wsash

L42 ANSWER 82 OF 109 MEDLINE
AN 94352867 MEDLINE
DN 94352867
TI Stem cell factor regulates human melanocyte-matrix interactions.
AU Scott G; Ewing J; Ryan D; Abboud C
CS Department of Dermatology, University of Rochester, School of Medicine and Dentistry, New York 14642..
NC AR-01882-01 (NIAMS)
HL-18208 (NHLBI)
CA-32737 (NCI)
+
SO PIGMENT CELL RESEARCH, **(1994 Feb)** 7 (1) 44-51.
Journal code: PIG. ISSN: 0893-5785.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199412
AB Stem cell factor (SCF) is hypothesized to play a critical role in the migration of melanocytes during embryogenesis because mutations in either the SCF gene, or its ligand, c-kit, result in defects in coat pigmentation in mice and in skin pigmentation in humans. In this report we directly show that SCF alters the adhesion and migration of human melanocytes to extracellular matrix (ECM) ligands and regulates integrin expression at the protein level. SCF decreased adhesion of neonatal and fetal cells to collagen IV, and increased attachment of fetal cells to laminin. Attachment of fetal cells to fibronectin was decreased, but was unchanged in neonatal cells. Flow cytometry analysis of neonatal melanocytes showed that SCF down-regulated the expression of the alpha 2 receptor, and up-regulated the expression of the alpha 3, alpha 5 and beta 1 integrin receptors. SCF down-regulated expression of alpha 2, alpha 5 and beta 1 integrins by fetal melanocytes, and up-regulated expression of the alpha v and alpha 3 integrin receptors. Analysis of melanocyte migration using time-lapse videomicroscopy showed that SCF significantly increased migration of neonatal, but not fetal, melanocytes on fibronectin (FN). We conclude that SCF regulates integrin expression at the protein level and that SCF has pleiotropic effects on melanocyte attachment and migration on ECM ligands. We suggest that this may be one mechanism by which SCF regulates melanocyte migration during development of the skin.
CT Check Tags: Comparative Study; Human; Support, U.S. Gov't, P.H.S.
Cell Adhesion: DE, drug effects
Cell Movement: DE, drug effects
Cells, Cultured

Collagen
*Extracellular Matrix: ME, metabolism
Fibronectins
Gene Expression Regulation: DE, drug effects
Gestational Age
Hematopoietic Cell Growth Factors: PD, pharmacology
*Hematopoietic Cell Growth Factors: PH, physiology
Infant, Newborn
Integrins: BI, biosynthesis
Integrins: GE, genetics
Laminin
Ligands
Melanocytes: CY, cytology
***Melanocytes: DE, drug effects**
Melanocytes: ME, metabolism
Skin: CY, cytology
***Skin: EM, embryology**
RN 9007-34-5 (Collagen)
CN 0 (Fibronectins); 0 (Hematopoietic Cell Growth Factors); 0 (Integrins); 0 (Laminin); 0 (Ligands); **0 (Stem Cell Factor)**

L42 ANSWER 83 OF 109 MEDLINE
AN 94352865 MEDLINE
DN 94352865
TI Effects of mutations at the W locus (c-kit) on inner ear pigmentation and function in the mouse.
AU Cable J; Huszar D; Jaenisch R; Steel K P
CS MRC Institute of Hearing Research, University Park, Nottingham, U.K.
SO PIGMENT CELL RESEARCH, **(1994 Feb)** 7 (1) 17-32.
Journal code: PIG. ISSN: 0893-5785.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199412
AB The W locus encodes a tyrosine kinase receptor, c-kit, which affects survival of melanoblasts from the neural crest. The primary cochlear defect in Viable Dominant Spotting (Wv/Wv) mutants is a lack of melanocytes within the stria vascularis (SV) associated with an endocochlear potential (EP) close to zero and hearing impairment. In this study, we compare inner ear pigmentation with cochlear potentials in three other W alleles (Wx, Wsh, and W41) and reveal an unequivocal correlation between presence of strial melanocytes and presence of an EP. Asymmetry was common, and 8.3% of Wsh/Wx, 25% of Wsh/Wsh, 60% of W41/Wx, and 69.2% of W41/W41 ears had a pigmented stria and an EP, while the remainder had no strial melanocytes and no EP. In those mutants that partially escaped the effects of the mutation, strial melanocytes rarely extended the entire length of the stria, but were confined to the middle and/or basal turns of the cochlea. The extent of strial pigmentation was unrelated to the EP value, which was measured from the basal turn only. Compound action potential (CAP) responses recorded from ears with an EP were variable and they showed greatly raised thresholds or were absent in all ears where the EP was close to zero. In controls, melanocytes in the vestibular part of the ear were found in the utricle, crus commune, and ampullae, whereas in many mutants only one or two of these regions were pigmented. There was a broad correlation between pigmentation of the stria and pigmentation of the vestibular region but this was not absolute. All W41/Wx, Wsh/Wsh, and W41/W41 mutants had some pigment on the pinna but, in contrast to controls where melanocytes were found in the epidermis and dermis of the pinna, pigment cells were reduced in number and generally restricted to the dermis. Injection of normal neural crest cells into 9.5-day-old mutant embryos increased the extent of skin pigmentation on the head and coat of adult chimeras and was associated with a small increase in the proportion of pigmented strias.
CT Check Tags: Animal; Comparative Study; Human; Support, Non-U.S. Gov't
Action Potentials

Alleles
Cell Movement
Chimera
*Cochlear Microphonic Potentials
Dog Diseases: GE, genetics
Dogs
Ear, External: PA, pathology
Fetal Tissue Transplantation
Hair Color: GE, genetics
Hearing Loss, Sensorineural: EM, embryology
*Hearing Loss, Sensorineural: GE, genetics
Hearing Loss, Sensorineural: PA, pathology
Hearing Loss, Sensorineural: VE, veterinary
Melanocytes: PA, pathology
Mice
Mice, Inbred CBA
Mice, Inbred C3H
Mice, Inbred C57BL
*Mice, Mutant Strains: GE, genetics
Neural Crest: PA, pathology
Neural Crest: TR, transplantation
Pigmentation Disorders: EM, embryology
***Pigmentation Disorders: GE, genetics**
Pigmentation Disorders: PA, pathology
Pigmentation Disorders: VE, veterinary
*Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins: PH, physiology
***Receptor Protein-Tyrosine Kinases: GE, genetics**
Receptor Protein-Tyrosine Kinases: PH, physiology
***Receptors, Colony-Stimulating Factor: GE, genetics**
Receptors, Colony-Stimulating Factor: PH, physiology
Skin Pigmentation: GE, genetics
Species Specificity
*Stria Vascularis: PA, pathology
Vestibule: EM, embryology
Vestibule: PA, pathology
Waardenburg's Syndrome: GE, genetics

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)
GEN c-kit; Wsh; Wv; W41; Wx; KIT

L42 ANSWER 84 OF 109 MEDLINE
AN 94336220 MEDLINE
DN 94336220
TI Instability at the W/c-kit locus in mice: analysis of melanocyte cell lines derived from reversion spots.
AU De Sepulveda P; Peyrieras N; Panthier J J
CS URA INRA de Genetique Moleculaire, Ecole Nationale Veterinaire d'Alfort, Maisons Alfort, France.
SO ONCOGENE, **(1994 Sep)** 9 (9) 2655-61.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199411
AB Mutations at the mouse W/c-kit locus have pleiotropic defects including impaired development of the melanocyte lineage. We have characterized the molecular basis of the Wei mutation. We show here that Wei is the result of a missense mutation in the ATP binding site domain of c-kit proto-oncogene which affects the tyrosine kinase function of the receptor. As a result, few melanoblasts survive during embryogenesis in heterozygous Wei/+ foetuses. Therefore the adult skin is partly devoid of differentiated pigmented cells giving rise to a mottled coat colour phenotype. However, three per cent of Wei/+ mice exhibit spots of

wild-type pigmentation on the coat which is otherwise of mutant phenotype. Such areas are known as phenotypic reversions. To dissect the molecular events responsible for the phenotypic instability of the Wei mutation, we have isolated pure cultures of continuously proliferating melanocytes from two independent reversion spots. These melanocyte lines, designated Wei-R1 and Wei-R2, were shown to exhibit none of the characteristics associated with transformed melanocytes. We have used a polymorphic restriction site generated by the Wei mutation to show that both melanocyte lines are still heterozygous at the W focus. Furthermore, Wei-R1 and Wei-R2 melanocytes express both the mutated and the wild-type c-kit RNA. These results indicate that the somatic mutation events responsible for reversion spots are not necessarily associated with loss of heterozygosity at the W/c-kit locus. Together with previous data, this points to the fact that several mechanisms account for the coat colour reversion phenotype.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Alleles
Cell Line
Chromosome Deletion
Chromosome Mapping
Hair Color
***Melanocytes: ME, metabolism**
*Mice: GE, genetics
Mice, Inbred C57BL
*Mutation
*Proto-Oncogene Proteins: GE, genetics
***Receptor Protein-Tyrosine Kinases: GE, genetics**
***Receptors, Colony-Stimulating Factor: GE, genetics**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)

GEN Wei; c-kit

L42 ANSWER 85 OF 109 MEDLINE

AN 94304416 MEDLINE

DN 94304416

TI Studies of the intracellular Ca2+ levels in human adult skin mast cells activated by the ligand for the human c-kit receptor and anti-IgE.

AU Columbo M; Botana L M; Horowitz E M; Lichtenstein L M; MacGlashan D W Jr

CS Department of Medicine, Johns Hopkins University School of Medicine, Johns Hopkins Asthma & Allergy Center, Baltimore, MD 21224.

NC AI20253 (NIAID)
AI7290 (NIAID)

SO BIOCHEMICAL PHARMACOLOGY, **(1994 Jun 15)** 47 (12) 2137-45.
Journal code: 9Z4. ISSN: 0006-2952.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199410

AB The human c-kit receptor ligand, rhSCF, is the only cytokine known to be active on human mast cells, but its intracellular signal transduction pathway is still unknown. We compared the effect of rhSCF on intracellular Ca2+ levels in purified (> 70% pure) adult skin mast cells with two other immunologic stimuli, namely, anti-IgE and substance P. Both rhSCF (1 microgram/mL) and anti-IgE (3 micrograms/mL) induced a rapid (< 20 sec) and sustained (T1/2 for decay > 10 min) increase in free cytosolic Ca2+ concentration. In contrast, substance P (5 microM) elicited a very rapid (< 1 sec) and transient (T1/2 for decay congruent to 5 sec) rise in intracellular Ca2+ levels. Intracellular cAMP levels were then increased by pharmacologic means to examine the role of the cyclic nucleotide in controlling the Ca2+ response in skin mast cells. A combination of the general phosphodiesterase inhibitor, isobutylmethylxanthine (IBMX) (200 microM) and the adenylate cyclase activator, forskolin (30 microM) was effective in inhibiting the Ca2+ response induced by rhSCF or anti-IgE (82 and 68% inhibition, respectively), while IBMX and forskolin alone were much less effective. The phosphodiesterase isozyme IV inhibitor, rolipram

(10 microM), variably affected the increase in Ca2+ levels induced by anti-IgE, but it exerted a significant inhibitory activity on anti-IgE- or rhSCF-induced response in the presence of forskolin (30 micrograms/mL) (33 and 67%, respectively). Two different protein kinase C (PKC) activators TPA (200 nM) and bryostatin 1 (200 nM) similarly inhibited rhSCF- (22 and 32%, respectively) and anti-IgE-induced (24 and 32%) Ca2+ response. Finally, the kinase inhibitor genistein (30 micrograms/mL) was a somewhat more effective inhibitor of the rise in intracellular Ca2+ induced by rhSCF (100%) than that activated by anti-IgE (54%) ($P < 0.05$). These data indicate that rhSCF and anti-IgE may act on human mast cells through a common pathway to increase free cytosolic Ca2+ levels and this effect is similarly modulated by various drugs.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
*Antibodies, Anti-Idiotypic: PD, pharmacology
*Calcium: AN, analysis
Cyclic AMP: AN, analysis
*Hematopoietic Cell Growth Factors: PD, pharmacology
Isoflavones: PD, pharmacology
*Mast Cells: ME, metabolism
Protein Kinase C: ME, metabolism
*Proto-Oncogene Proteins: DE, drug effects
***Receptor Protein-Tyrosine Kinases: DE, drug effects**
***Receptors, Colony-Stimulating Factor: DE, drug effects**
Recombinant Proteins: PD, pharmacology
***Skin: ME, metabolism**
Substance P: PD, pharmacology
Time Factors

RN 33507-63-0 (Substance P); 446-72-0 (Genistein); 60-92-4 (Cyclic AMP); 7440-70-2 (Calcium)

CN EC 2.7.1.- (Protein Kinase C); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (anti-IgE); 0 (Antibodies, Anti-Idiotypic); 0 (Hematopoietic Cell Growth Factors); 0 (Isoflavones); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); 0 (Recombinant Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 86 OF 109 MEDLINE
AN 94264303 MEDLINE
DN 94264303
TI C-kit gene is expressed by skin mast cells in embryos but not in puppies of Wsh/Wsh mice: age-dependent abolishment of c-kit gene expression.
AU Yamazaki M; Tsujimura T; Morii E; Isozaki K; Onoue H; Nomura S; Kitamura Y
CS Department of Pathology, Osaka University Medical School, Japan.
SO BLOOD, **(1994 Jun 15)** 83 (12) 3509-16.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199409
AB The Wsh is a mutant allele at the W (c-kit) locus of mice, but no significant abnormalities are found at the coding region of the Wsh allele. Since cultured mast cells derived from the spleen of Wsh/Wsh mice do not express messenger RNA (mRNA) of c-kit, we studied the interrelation between the number of mast cells and the magnitude of c-kit mRNA expression in the skin of Wsh/Wsh mice of various ages. The number of mast cells in the skin of Wsh/Wsh embryos of 18 days postcoitum (pc) was approximately 40% that of normal control (+/+) embryos, but the number of mast cells decreased exponentially after birth; the number dropped to 0.6% that of +/+ mice at day 150 after birth. A weak but apparent signal of c-kit mRNA was detectable in the skin of 18-day pc Wsh/Wsh embryos by RNase protection assay but not in the skin of 5-day-old Wsh/Wsh mice. The number of c-kit protein-containing cells was significantly greater in the skin of 18-day pc Wsh/Wsh embryos than in the skin of 5-day-old Wsh/Wsh mice. The abolishment of c-kit mRNA expression appeared to be specific, because the expression of mast cell carboxypeptidase A mRNA but not of

c-kit mRNA was detectable by in situ hybridization in skin mast cells of 5-day-old Wsh/Wsh mice. Taken together, the expression of c-kit mRNA was abolished first, then the content of c-kit protein dropped to undetectable levels, and then the disappearance of Wsh/Wsh mast cells themselves followed.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Age Factors
Animals, Newborn
Base Sequence
*Gene Expression Regulation
*Mast Cells: ME, metabolism
Mice
Mice, Inbred C57BL
Molecular Sequence Data
Mutation
Pregnancy
Proto-Oncogene Proteins: DF, deficiency
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
Receptor Protein-Tyrosine Kinases: DF, deficiency
***Receptor Protein-Tyrosine Kinases: GE, genetics**
Receptors, Colony-Stimulating Factor: DF, deficiency
***Receptors, Colony-Stimulating Factor: GE, genetics**
RNA, Messenger: AN, analysis
Skin: CY, cytology
Skin: EM, embryology
***Skin: ME, metabolism**

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); 0 (RNA, Messenger)

L42 ANSWER 87 OF 109 MEDLINE
AN 94137580 MEDLINE
DN 94137580
TI Association of malignant melanoma and germ cell tumour [letter].
AU Dwyer C M; Dick D
SO BRITISH JOURNAL OF DERMATOLOGY, **(1994 Jan)** 130 (1) 129.
Journal code: AW0. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT Letter
LA English
FS Priority Journals
EM 199405
CT Check Tags: Case Report; Female; Human
Adult
*Melanoma: GE, genetics
*Neoplasms, Multiple Primary: GE, genetics
*Ovarian Neoplasms: GE, genetics
Proto-Oncogene Proteins: GE, genetics
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptors, Cell Surface: GE, genetics
Receptors, Colony-Stimulating Factor: GE, genetics
***Skin Neoplasms: GE, genetics**
*Teratoma: GE, genetics
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface); 0 (Receptors, Colony-Stimulating Factor)

L42 ANSWER 88 OF 109 MEDLINE
AN 94061059 MEDLINE
DN 94061059
TI A recurrent deletion in the KIT (mast/stem cell growth factor receptor) proto-oncogene is a frequent cause of human piebaldism.
AU Spritz R A; Holmes S A; Berg S Z; Nordlund J J; Fukai K
CS Department of Medical Genetics, University of Wisconsin, Madison 53706.
NC AR39892 (NIAMS)

SO HUMAN MOLECULAR GENETICS, **(1993 Sep)** 2 (9) 1499-500.
Journal code: BRC. ISSN: 0964-6906.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Base Sequence
DNA: GE, genetics
Frameshift Mutation
Molecular Sequence Data
***Piebaldism: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
***Receptor Protein-Tyrosine Kinases: GE, genetics**
***Receptors, Colony-Stimulating Factor: GE, genetics**
*Sequence Deletion
RN 9007-49-2 (DNA)
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor)
GEN KIT

L42 ANSWER 89 OF 109 MEDLINE
AN 93380750 MEDLINE
DN 93380750
TI Polymerase chain reaction detection of a novel human KIT (mast/stem cell growth factor receptor) gene polymorphism by single-strand conformation polymorphism analysis or by SmaI or BstNI cleavage.
AU Spritz R A; Holmes S A
CS Laboratory of Genetics, University of Wisconsin, Madison 53706..
NC AR39892 (NIAMS)
SO HUMAN GENETICS, **(1993 Sep)** 92 (2) 208-9.
Journal code: GED. ISSN: 0340-6717.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199312
AB We describe a common single-base polymorphism of the KIT gene that alters both SmaI and BstNI restriction sites, but is most easily detected as a single-strand conformation polymorphism (SSCP) using the polymerase chain reaction (PCR).
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alleles
Base Sequence
Chromosomes, Human, Pair 4
Deoxyribonucleases, Type II Site-Specific
DNA, Single-Stranded: AN, analysis
Gene Frequency
*Hematopoietic Cell Growth Factors
Molecular Sequence Data
Nucleic Acid Conformation
***Piebaldism: GE, genetics**
Point Mutation
Polymerase Chain Reaction
*Polymorphism, Restriction Fragment Length
***Protein-Tyrosine Kinase: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
***Receptors, Cell Surface: GE, genetics**
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 3.1.21.- (endodeoxyribonuclease BstNI); EC 3.1.21.- (endodeoxyribonuclease XmaI); EC 3.1.21.4 (Deoxyribonucleases, Type II Site-Specific); 0 (DNA, Single-Stranded); 0

(Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface); **0 (Stem Cell Factor)**

L42 ANSWER 90 OF 109 MEDLINE
AN 93257670 MEDLINE
DN 93257670
TI Mast cell number in the skin of heterozygotes reflects the molecular nature of c-kit mutation.
AU Tsujimura T; Koshimizu U; Katoh H; Isozaki K; Kanakura Y; Tono T; Adachi S; Kasugai T; Tei H; Nishimune Y; et al
CS Department of Pathology, Medical School, Osaka University, Japan.
SO BLOOD, **(1993 May 15)** 81 (10) 2530-8.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199308
AB The W locus of mice encodes the c-kit receptor tyrosine kinase. Heterozygous WJic/+ and Wn/+ mice and homozygous Wf/Wf mice were similar in appearance; all of them have large depigmented areas lacking any well-defined pattern. The WJic, Wn, and Wf mutant alleles were characterized and their molecular nature was correlated with the mast cell differentiation in the skin and the biologic features of cultured mast cell (CMC). All WJic, Wn, and Wf were point mutations at the tyrosine kinase domain, and c-kit mRNA was normally transcribed from all of them. The mature 145-Kd form of the c-kit protein was produced from the WJic and Wf alleles, but not from the Wn allele. c-kit proteins produced by the WJic or Wf allele were expressed on the surface of CMCs, but those of the Wn allele were not. When double heterozygous mice were produced between W and WJic and between W and Wn, both W/WJic and W/Wn mice lacked skin mast cells. W/WJic CMCs and W/Wn CMCs did not survive in the coculture with fibroblasts. W/WJic CMCs normally attached to fibroblasts, but W/Wn CMCs did not. The defect of W/Wn CMCs in the attachment was attributed to the deficient extracellular expression of the c-kit protein. The number of skin mast cells was compared among WJic/+, Wn/+, Wf/+, and Wf/Wf mice. Mast cells decreased in WJic/+ and Wf/Wf mice, but not in Wn/+ and Wf/+ mice. Although the Wn was a point mutation at the kinase domain, the biologic effect of the Wn was comparable with that of the W mutant allele, which produces truncated c-kit protein without the transmembrane domain. The weak phenotype of Wn/+ mice may be explained by the deficient extracellular expression of c-kit proteins produced by the Wn allele. When WJic/WJic, Wn/Wn, and Wf/Wf CMCs were stimulated by the recombinant c-kit ligand, autophosphorylation activity was observed only in Wf/Wf CMCs. This result was consistent with the weak biologic effect of the Wf mutant allele.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Adenosine Triphosphate: ME, metabolism
Alleles
Base Sequence
Cell Survival
Cells, Cultured
Crosses, Genetic
Erythrocyte Count
Fibroblasts: CY, cytology
Fibroblasts: PH, physiology
Genotype
Hair Color: GE, genetics
*Heterozygote
Homozygote
*Leukocyte Count
*Mast Cells: CY, cytology
Mast Cells: PH, physiology
Mice
Mice, Inbred C57BL
Mice, Mutant Strains

Molecular Sequence Data
Oligodeoxyribonucleotides
*Point Mutation
Polymerase Chain Reaction: MT, methods
***Protein-Tyrosine Kinase: GE, genetics**
Protein-Tyrosine Kinase: ME, metabolism
*Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins: ME, metabolism
*Proto-Oncogenes
***Skin: CY, cytology**
Skin: PH, physiology
Skin Physiology
RN 56-65-5 (Adenosine Triphosphate)
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Oligodeoxyribonucleotides); 0 (Proto-Oncogene Proteins)
GEN c-kit

L42 ANSWER 91 OF 109 MEDLINE
AN 93235929 MEDLINE
DN 93235929
TI Absence of immature mast cells in the skin of Ws/Ws rats with a small deletion at tyrosine kinase domain of the c-kit gene.
AU Onoue H; Maeyama K; Nomura S; Kasugai T; Tei H; Kim H M; Watanabe T; Kitamura Y
CS Department of Pathology, Osaka University Medical School, Japan.
SO AMERICAN JOURNAL OF PATHOLOGY, **(1993 Apr)** 142 (4) 1001-7.
Journal code: 3RS. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199307
AB Ws/Ws rats have a small deletion at the tyrosine kinase domain of the c-kit gene, and practically no mast cells were detectable when the tissues were stained with alcian blue. Because alcian blue stains proteoglycans, there is a possibility that immature mast cells that do not contain a sufficient amount of proteoglycans are not detectable by this method. We examined this possibility by using other markers of mast cells. The histamine content in the skin of Ws/Ws rats was 0.3% that of control normal (+/+) rats. Because the number of alcian blue-positive mast cells in the skin of Ws/Ws rats was also 0.3% that of +/+ rats, histamine in the skin seemed to be concentrated to alcian blue-positive mast cells. Mast cells in the skin of +/+ rats express messenger RNA of Fc epsilon RI beta-subunit and c-kit protein. Because c-kit messenger RNA was normally expressed at least in the brain of Ws/Ws rats despite the small deletion, we examined the expression of Fc epsilon RI beta-subunit and c-kit messenger RNA in the skin and stomach of Ws/Ws rats by reverse transcriptase modification of polymerase chain reaction. Expression of either Fc epsilon RI beta-subunit or c-kit messenger RNA in the skin and stomach of Ws/Ws rats was estimated to be less than 1% that of +/+ rats. Moreover no Fc epsilon RI beta-subunit-expressing and no c-kit-expressing cells were detectable in the skin of Ws/Ws rats by in situ hybridization histochemistry. The present result suggests the absence of immature mast cells in tissues of Ws/Ws rats.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Base Sequence
Blotting, Southern
Cell Aging
*Gene Deletion
Histamine: ME, metabolism
In Situ Hybridization
*Mast Cells: PA, pathology
Mast Cells: PH, physiology
Molecular Sequence Data
Oligonucleotide Probes: GE, genetics

***Protein-Tyrosine Kinase: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
Rats
*Rats, Mutant Strains: GE, genetics
Receptors, IgE: GE, genetics
RNA, Messenger: ME, metabolism
***Skin: PA, pathology**
Tissue Distribution
RN 51-45-6 (Histamine)
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Oligonucleotide Probes); 0 (Proto-Oncogene Proteins); 0 (Receptors, IgE); 0 (RNA, Messenger)

L42 ANSWER 92 OF 109 MEDLINE
AN 93226002 MEDLINE
DN 93226002
TI Altered metabolism of mast-cell growth factor (c-kit ligand) in cutaneous mastocytosis.
AU Longley B J Jr; Morganroth G S; Tyrrell L; Ding T G; Anderson D M; Williams D E; Halaban R
CS Department of Dermatology, Yale University School of Medicine, New Haven, Conn 06510..
NC 1 R29AR40514-01 (NIAMS)
5 R29CA44542-03 (NCI)
SO NEW ENGLAND JOURNAL OF MEDICINE, **(1993 May 6)** 328 (18) 1302-7.
Journal code: NOW. ISSN: 0028-4793.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199307
AB BACKGROUND AND METHODS. The lesions of cutaneous mastocytosis are characterized by dermal infiltrates of mast cells and may appear **hyperpigmented** because of the presence of increased levels of epidermal melanin. Mast-cell growth factor, the ligand for the product of the c-kit proto-oncogene, stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. We therefore looked for the expression of the mast-cell growth factor gene in the skin of patients with cutaneous mastocytosis using immunohistochemical techniques and the polymerase chain reaction. RESULTS. In the skin of normal subjects and those with unrelated diseases, immunoreactive mast-cell growth factor was associated with keratinocytes and scattered dermal cells, a pattern consistent with cell-bound mast-cell growth factor. In skin samples containing lesions and in clinically normal skin from patients with mastocytosis, however, mast-cell growth factor was also found free in the dermis and in the extracellular spaces between keratinocytes, suggesting the presence of a soluble form of this protein. Messenger RNA (mRNA) that can encode soluble mast-cell growth factor was present in the skin of patients as well as in that of normal control subjects. No sequence abnormalities were detected in mRNA for mast-cell growth factor from one patient. CONCLUSIONS. The altered distribution of mast-cell growth factor in the skin of patients with cutaneous mastocytosis is consistent with abnormal production of the soluble form of this factor. This abnormality is probably due to increased proteolytic processing, since it was not explained by differences in the splicing or sequence of mast-cell growth factor mRNA in the patients. Soluble mast-cell growth factor may cause the characteristic accumulation of mast cells and the **hyperpigmentation** of skin found in cutaneous mastocytosis. These findings suggest that some forms of mastocytosis represent reactive hyperplasia rather than mast-cell neoplasia.
CT Check Tags: Case Report; Female; Human; Male; Support, U.S. Gov't, P.H.S.
Adult
Base Sequence
Cells, Cultured
Hematopoietic Cell Growth Factors: GE, genetics
*Hematopoietic Cell Growth Factors: ME, metabolism

Infant, Newborn
Keratinocytes: ME, metabolism
Ligands
***Mastocytosis: ME, metabolism**
Mastocytosis: PA, pathology
Middle Age
Molecular Sequence Data
Oligonucleotide Probes
Polymerase Chain Reaction
RNA, Messenger: AN, analysis
***Skin: ME, metabolism**
Skin: PA, pathology
CN 0 (Hematopoietic Cell Growth Factors); 0 (Ligands); 0 (Oligonucleotide Probes); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

L42 ANSWER 93 OF 109 MEDLINE
AN 93083426 MEDLINE
DN 93083426
TI TRP-2/DT, a new early melanoblast marker, shows that steel growth factor (c-kit ligand) is a survival factor.
AU Steel K P; Davidson D R; Jackson I J
CS MRC Institute of Hearing Research, University Park, Nottingham, UK.
SO DEVELOPMENT, **(1992 Aug)** 115 (4) 1111-9.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
AB We have used a probe derived from TRP-2/DT to detect migratory melanoblasts shortly after they emerge from the neural crest, as early as 10 days post coitum (dpc). TRP-2/DT expression is otherwise restricted to the presumptive pigmented retinal epithelium, the developing telencephalon and the endolymphatic duct. The pattern of steel and c-kit hybridisation in the developing brain differed from that of TRP-2. TRP-1 and tyrosinase probes also detected melanoblasts but were both expressed later in development than TRP-2. We used the TRP-2/DT probe to investigate the way that the Steel-dickie (Sld) mutation interferes with melanocyte development, and found that the membrane-bound steel growth factor which is missing in Sld/Sld mutants is necessary for the survival of melanoblasts but not for their early migration and initial differentiation.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Differentiation: PH, physiology
Cell Movement: PH, physiology
Cell Survival: PH, physiology
*Central Nervous System: EM, embryology
Cochlea: EM, embryology
Eye: EM, embryology
*Fetal Development: GE, genetics
*Gene Expression: PH, physiology
Genetic Markers: PH, physiology
Genotype
Harderian Gland: EM, embryology
*Hematopoietic Cell Growth Factors: GE, genetics
***Isomerases: GE, genetics**
***Melanocytes: PH, physiology**
Mice
Mice, Mutant Strains
Molecular Probe Techniques
Nucleic Acid Hybridization
Proto-Oncogene Proteins: GE, genetics
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 5. (Isomerases); EC 5.3.2.- (dopachrome oxidoreductase); 0 (Genetic Markers); 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 94 OF 109 MEDLINE
AN 93072064 MEDLINE
DN 93072064
TI Deletion of the KIT and PDGFRA genes in a patient with piebaldism.
AU Spritz R A; Droetto S; Fukushima Y
CS Department of Medical Genetics, University of Wisconsin, Madison.
NC AR 39892 (NIAMS)
SO AMERICAN JOURNAL OF MEDICAL GENETICS, **(1992 Nov 1)** 44 (4) 492-5.
Journal code: 3L4. ISSN: 0148-7299.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199302
AB We have previously shown that human piebaldism results from mutations of the KIT gene, which encodes the receptor for the mast/stem cell growth factor and is located in chromosome segment 4q12. Using DNA of a patient with piebaldism, mental retardation, and multiple congenital anomalies associated with a 46,XY,del(4) (q12q21.1) karyotype, we carried out quantitative Southern blot hybridization analyses of the KIT gene and the adjacent PDGFRA (platelet-derived growth factor receptor alpha subunit) genes. The patient was hemizygous for both the KIT and PDGFRA genes, indicating that both of these genes are included within the deleted region. Therefore, deletion of the KIT and PDGFRA genes may account for the piebald phenotype in this patient.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Base Sequence
Cells, Cultured
*Chromosomes, Human, Pair 4
DNA Probes
DNA, Single-Stranded
*Gene Deletion
Mental Retardation: GE, genetics
Molecular Sequence Data
***Piebaldism: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
***Receptors, Platelet-Derived Growth Factor: GE, genetics**
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptors, Platelet-Derived Growth Factor); 0 (DNA Probes); 0 (DNA, Single-Stranded); 0 (Proto-Oncogene Proteins)
GEN KIT; PDGFRA

L42 ANSWER 95 OF 109 MEDLINE
AN 93035369 MEDLINE
DN 93035369
TI Mutations of the KIT (mast/stem cell growth factor receptor) proto-oncogene account for a continuous range of phenotypes in human piebaldism [published erratum appears in Am J Hum Genet 1993 Mar;52(3):654].
AU Spritz R A; Holmes S A; Ramesar R; Greenberg J; Curtis D; Beighton P
CS Department of Medical Genetics, University of Wisconsin, Madison 53706.
NC AR 39892 (NIAMS)
SO AMERICAN JOURNAL OF HUMAN GENETICS, **(1992 Nov)** 51 (5) 1058-65.
Journal code: 3IM. ISSN: 0002-9297.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199301
AB Piebaldism is a rare autosomal dominant disorder of pigmentation, characterized by congenital patches of white skin and hair from which melanocytes are absent. We have previously shown that piebaldism can result from missense and frameshift mutations of the KIT proto-oncogene, which encodes the cellular receptor tyrosine kinase for the mast/stem cell growth factor. Here, we report two novel KIT mutations associated with

human piebaldism. A proximal frameshift is associated with a mild piebald phenotype, and a splice-junction mutation is associated with a highly variable piebald phenotype. We discuss the apparent relationship between the predicted impact of specific KIT mutations on total KIT-dependent signal transduction and the severity of the resultant piebald phenotypes.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Base Sequence
Blotting, Southern
Frameshift Mutation
Molecular Sequence Data
Mutation: GE, genetics
Pedigree
Phenotype
***Piebaldism: GE, genetics**
Polymerase Chain Reaction
Protein-Tyrosine Kinase: CH, chemistry
***Protein-Tyrosine Kinase: GE, genetics**
Proto-Oncogene Proteins: CH, chemistry
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
Receptors, Cell Surface: CH, chemistry
***Receptors, Cell Surface: GE, genetics**

CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface)

GEN KIT

L42 ANSWER 96 OF 109 MEDLINE
AN 92394673 MEDLINE
DN 92394673
TI Progression of human cutaneous melanoma is associated with loss of expression of c-kit proto-oncogene receptor.
AU Natali P G; Nicotra M R; Winkler A B; Cavaliere R; Bigotti A; Ullrich A
CS Regina Elena Cancer Institute, Rome, Italy.
SO INTERNATIONAL JOURNAL OF CANCER, **(1992 Sep 9)** 52 (2) 197-201.
Journal code: GQU. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199212
AB Mutations at the white spotting (w) locus in mice have deleterious effects on germ cells, melanocytes and hematopoietic stem cells. The w locus encodes the c-kit tyrosine-kinase receptor whose ligand is the product of the SI locus. Using monoclonal antibodies (MAb(s)) to the extracellular domain, we have evaluated the expression of c-kit in normal and transformed melanocytes. This cell lineage synthesizes a receptor with a mw of 145 kDa. The gene product is expressed in epidermal melanocytes and in a fraction of nevocytic and blue nevi. In primary melanomas, loss of the receptor is observed in more invasive lesions. Only 30% of the metastatic lesions express detectable levels of the receptor. These findings demonstrate that the c-kit product is down-regulated in melanocytes following malignant transformation. The functional relevance of this modulation remains to be evaluated.

CT Check Tags: Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal
Gene Expression Regulation, Neoplastic
***Melanocytes: CH, chemistry**
*Melanoma: CH, chemistry
Melanoma: PA, pathology
Melanoma: SC, secondary
*Proto-Oncogene Proteins: AN, analysis
***Receptors, Cell Surface: AN, analysis**
***Skin Neoplasms: CH, chemistry**

Skin Neoplasms: PA, pathology
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Antibodies, Monoclonal); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface)

L42 ANSWER 97 OF 109 MEDLINE
AN 92391860 MEDLINE
DN 92391860
TI Stem cell factor/c-kit interaction in primordial germ cell, melanoblast and hematopoietic progenitors.
AU Miura N; Suda T
CS First Dept. of Internal Medicine, Faculty of Medicine, University of Tokyo.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], **(1992 Sep)** 19 (11) 1777-85.
Journal code: 6T8. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals; Cancer Journals
EM 199212
AB Mutation at S1 or W loci are characterized by lacks of pigmentation, gametogenesis and hematopoiesis. Stem cell factor and its receptor, which is encoded by c-kit proto-oncogene, play an important role in the survival and proliferation of these primitive cells. Primordial germ cell is maintained and expanded on cells transfected with membrane-bound SCF gene. Pigmentation of mouse embryo is influenced by administration of monoclonal antibody for c-kit product, ACK 2, because of inhibition of melanoblast migration to epidermal tissue. Moreover, hematopoietic progenitors are considered to be maintained and expanded in liquid culture in the presence of SCF and other growth factors. All of these primitive cells express c-kit product and the direct action of SCF is expected. However, two types of SCF, soluble form and membrane-bound form, exist and the physiological significance of these forms in vivo remain unsolved.
CT Check Tags: Animal
Cell Communication
Cell Division
English Abstract
Erythroid Progenitor Cells: PH, physiology
Hematopoiesis
Hematopoietic Cell Growth Factors: CH, chemistry
Hematopoietic Cell Growth Factors: GE, genetics
*Hematopoietic Cell Growth Factors: PH, physiology
***Hematopoietic Stem Cells: PH, physiology**
Mast Cells: CY, cytology
***Melanocytes: PH, physiology**
Mice
Proto-Oncogene Proteins: PH, physiology
Receptors, Cell Surface: PH, physiology
CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Hematopoietic Cell Growth Factors); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface); **0 (Stem Cell Factor)**

L42 ANSWER 98 OF 109 MEDLINE
AN 92366553 MEDLINE
DN 92366553
TI Spontaneous malignant transformation of melanocytes explanted from Wf/Wf mice with a Kit kinase-domain mutation.
AU Larue L; Dougherty N; Porter S; Mintz B
CS Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA 19111.
NC HD-01646 (NICHD)
CA-42560 (NCI)
CA-06927 (NCI)
+
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1992 Aug 15)** 89 (16) 7816-20.

Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199211
AB The W/Kit mouse locus, affecting proliferation and survival of pigment cells, blood cells, and germ cells, is known to encode a tyrosine kinase growth factor receptor and is considered a protooncogene; yet it has not heretofore been causally implicated in any malignancies of those cells. The Wf/Wf mutant mouse coat comprises viable and inviable melanoblast clones, seen ultimately as pigmented and white transverse stripes--the latter more prominent. Judging from the pattern, all clones initially expand, and the inviable ones then undergo programmed cell death prenatally. To observe skin melanocytes of the viable clones during extended proliferation, the cells were explanted from individual young mice. An unusually large number of primary explants failed to survive--a result consistent with a growth handicap. In 3 of the 10 surviving cell lines, many cells spontaneously underwent a series of striking changes with the classic features of transformation. The two transformed lines that have been tested by grafting to immunosuppressed hosts formed undifferentiated invasive tumors compatible with malignant amelanotic melanoma. None of our 52 other melanocyte lines of the coisogenic wild-type strain and 13 other natural genotypes have become transformed under the same culture conditions. Molecular analysis of the Wf gene revealed a single change from wild-type: a point mutation affecting the catalytic region in the kinase domain of the Kit protein. The apparent growth disadvantage due to the mutation may allow selection for melanocytes mobilizing more efficient pathways, thus leading to neoplasia. Production of both viable and inviable melanoblast clones is unlikely to be due only to the kinase mutation; possibly the degree, duration, and consistency of expression of this locus may be controlled by cis elements outside the coding region.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Base Sequence
Cell Death
Cell Line
*Cell Transformation, Neoplastic: GE, genetics
Cells, Cultured
*Genes, Dominant
Genotype
***Melanocytes: CY, cytology**
Melanocytes: DE, drug effects
***Melanocytes: PA, pathology**
*Melanoma, Experimental: GE, genetics
Melanoma, Experimental: PA, pathology
Mice
Mice, Inbred C3H
Mice, Mutant Strains
Molecular Sequence Data
*Mutation
Oligodeoxyribonucleotides
***Protein-Tyrosine Kinase: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
***Skin Neoplasms: GE, genetics**
Skin Neoplasms: PA, pathology
Tetradecanoylphorbol Acetate: PD, pharmacology
RN 16561-29-8 (Tetradecanoylphorbol Acetate)
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Oligodeoxyribonucleotides); 0 (Proto-Oncogene Proteins)
GEN Kit; v-kit

L42 ANSWER 99 OF 109 MEDLINE
AN 92359118 MEDLINE

DN 92359118
TI Effect of the c-kit codon 584 Phe----Leu substitution demonstrated in human piebaldism [letter; comment].
CM Comment on: Am J Hum Genet 1992 Feb;50(2):261-9
AU Fleischman R A
SO AMERICAN JOURNAL OF HUMAN GENETICS, **(1992 Sep)** 51 (3) 677-8.
Journal code: 3IM. ISSN: 0002-9297.
CY United States
DT Commentary
Letter
LA English
FS Priority Journals
EM 199211
CT Check Tags: Human
Amino Acid Sequence
Codon: GE, genetics
Consensus Sequence
Molecular Sequence Data
Mutation: GE, genetics
***Piebaldism: GE, genetics**
***Protein-Tyrosine Kinase: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Codon); 0 (Proto-Oncogene Proteins)
GEN c-kit

L42 ANSWER 100 OF 109 MEDLINE
AN 92329930 MEDLINE
DN 92329930
TI Nonhematopoietic tumor cell lines express stem cell factor and display c-kit receptors.
AU Turner A M; Zsebo K M; Martin F; Jacobsen F W; Bennett L G; Broudy V C
CS Department of Medicine, University of Washington, Seattle 98195.
NC DK31232 (NIDDK)
SO BLOOD, **(1992 Jul 15)** 80 (2) 374-81.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199210
AB Human stem cell factor (SCF) acts in the presence of other growth factors to stimulate the growth of primitive hematopoietic progenitor cells. These effects are performed by activation of the SCF receptor, c-kit. Because of the potential use of SCF in patients undergoing chemotherapy and bone marrow transplantation, the effect of SCF on nonhematopoietic tumors requires investigation. To determine whether human tumor cell lines display c-kit receptors, we performed binding experiments with 125I-SCF on a breast carcinoma cell line (Du4475), a gastric carcinoma cell line (KATO III), a melanoma cell line (HTT144), as well as two small cell lung carcinoma cell lines (H69 and H128). The biologic effect of SCF on tumor cell lines was assessed by its ability to stimulate tritiated thymidine uptake and to enhance colony growth in methylcellulose. The breast carcinoma cell line, Du4475, as well as two small cell lung carcinoma cell lines, H69 and H128, exhibit high-affinity c-kit receptors with approximate binding affinities of 40, 100, and 90 pmol/L, respectively. The number of high-affinity receptors per cell ranged from 700 to 9,500. The gastric carcinoma cell line, as well as the melanoma cell line, showed trace binding of 125I-SCF. In the presence of SCF alone, or in combination with granulocyte-macrophage colony-stimulating factor or interleukin-3, there was less than a 17% increase in the colony growth of Du4475, H69, or H128 cell lines. Postulating that the lack of growth response could be secondary to endogenous SCF production by the tumor cell lines, we used an RNAse protection assay to determine whether the tumor cell lines contain SCF messenger RNA (mRNA). In addition, we tested tumor cell line

supernatants for the presence of secreted SCF protein by enzyme immunoassay, and analyzed the tumor cell lines for membrane-bound SCF by indirect immunofluorescence. Our results show that the Du4475, H69, and H128 cell lines, as well as a melanoma cell line (HTT144), have multiple copies of SCF mRNA. Soluble SCF protein was detected in the cell supernatants in the Du4475 and H69 cell lines and SCF was found on the surface of all four cell lines. These data show that some human solid tumor cell lines display high-affinity c-kit receptors and produce SCF, which can be detected on the cell surface. These results suggest the possibility that autocrine production of SCF by c-kit receptor-bearing tumor cells may enhance cell growth in tumor cell lines.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Division: DE, drug effects
Cell Line
DNA Replication: DE, drug effects
Fluorescent Antibody Technique
Granulocyte-Macrophage Colony-Stimulating Factor: PD, pharmacology
*Hematopoietic Cell Growth Factors: ME, metabolism
Hematopoietic Cell Growth Factors: PD, pharmacology
Interleukin-3: PD, pharmacology
Kinetics
*Melanoma: ME, metabolism
Mice
Proto-Oncogene Proteins: AN, analysis
Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogene Proteins: ME, metabolism
*Proto-Oncogenes
***Receptors, Cell Surface: ME, metabolism**
Recombinant Proteins: ME, metabolism
Recombinant Proteins: PD, pharmacology
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
***Skin Neoplasms: ME, metabolism**
Tumor Cells, Cultured

RN 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Hematopoietic Cell Growth Factors); 0 (Interleukin-3); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface); 0 (Recombinant Proteins); 0 (RNA, Messenger); **0 (Stem Cell Factor)**

GEN c-kit

L42 ANSWER 101 OF 109 MEDLINE

AN 92291284 MEDLINE

DN 92291284

TI Human piebald trait resulting from a dominant negative mutant allele of the c-kit membrane receptor gene.

AU Fleischman R A

CS Simmons Cancer Center, Department of Medicine, University of Texas, Southwestern Medical Center, Dallas 75235.

SO JOURNAL OF CLINICAL INVESTIGATION, **(1992 Jun)** 89 (6) 1713-7.
Journal code: HS7. ISSN: 0021-9738.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199209

AB Human piebald trait is an autosomal dominant defect in melanocyte development characterized by patches of hypopigmented skin and hair. Although the molecular basis of piebaldism has been unclear, a phenotypically similar "dominant spotting" of mice is caused by mutations in the murine c-kit protooncogene. In this regard, one piebald case with a point mutation and another with a deletion of c-kit have been reported, although a polymorphism or the involvement of a closely linked gene could not be excluded. To confirm the hypothesis that piebaldism results from mutations in the human gene, c-kit exons were amplified by polymerase

chain reaction from the DNA of 10 affected subjects and screened for nucleotide changes by single-stranded conformation polymorphism analysis. In one subject with a variant single-stranded conformation polymorphism pattern for the first exon encoding the kinase domain, DNA sequencing demonstrated a missense mutation (Glu583----Lys). This mutation is identical to the mouse W37 mutation which abolishes autophosphorylation of the protein product and causes more extensive depigmentation than "null" mutations. In accord with this "dominant negative" effect, the identical mutation in this human kindred is associated with unusually extensive depigmentation. Thus, the finding of a piebald subject with a mutation that impairs receptor activity strongly implicates the c-kit gene in the molecular pathogenesis of this human developmental defect.

CT Check Tags: Human; Support, Non-U.S. Gov't
Alleles
Amino Acid Sequence
Base Sequence
DNA
Genes, Dominant
Molecular Sequence Data
Mutation
Phenotype
***Piebaldism: GE, genetics**
Polymerase Chain Reaction
*Proto-Oncogene Proteins: GE, genetics
***Receptors, Cell Surface: GE, genetics**
Sequence Homology, Nucleic Acid

RN 9007-49-2 (DNA)

CN **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface)

L42 ANSWER 102 OF 109 MEDLINE

AN 92241397 MEDLINE

DN 92241397

TI The ret oncogene can induce melanogenesis and melanocyte development in Wv/Wv mice.

AU Iwamoto T; Takahashi M; Ohbayashi M; Nakashima I

CS Department of Immunology, Nagoya University School of Medicine, Japan.

SO EXPERIMENTAL CELL RESEARCH, **(1992 Jun)** 200 (2) 410-5.
Journal code: EPB. ISSN: 0014-4827.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199208

AB We recently reported the establishment of transgenic mouse lines carrying the mouse metallothionein/ret fusion gene in which severe melanosis and melanocytic tumors developed. In the present study, we demonstrate that a significant number of pigmented hairs developed in Wv/Wv mice crossed to one of the transgenic mouse lines. The pigmented hair of Wv/Wv mice carrying the ret oncogene did not lose color during aging and reappeared after shaving, indicating that the melanocytes in the hair follicle function. The melanocytic tumors also developed in these mice, although the incidence was lower than that in the wild transgenic mice. Furthermore, the neutral tube culture of mouse embryos indicated that neural crest cells of the transgenic mice gave rise to a cell population that autonomously produced melanin even in the absence of melanocyte stimulating hormone. These results strongly suggested that the introduced ret oncogene could compensate for the defect of c-kit in Wv mice during both embryogenesis and postnatal life and induce a high level of melanin synthesis in the process of melanocyte development.

CT Check Tags: Animal; In Vitro; Support, Non-U.S. Gov't
Aging
Cell Differentiation
Cells, Cultured
***Melanins: BI, biosynthesis**
***Melanocytes: CY, cytology**

Mice
Mice, Transgenic
*Neoplasms, Experimental: GE, genetics
Nervous System: CY, cytology
Nervous System: EM, embryology
*Protein-Tyrosine Kinase: PH, physiology
*Proto-Oncogene Proteins: PH, physiology
*Proto-Oncogenes
*Receptors, Cell Surface: PH, physiology
Signal Transduction
Skin Pigmentation
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (proto-oncogene protein ret); 0 (Melanins); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface)
GEN ret; kit

L42 ANSWER 103 OF 109 MEDLINE
AN 92199350 MEDLINE
DN 92199350
TI c-Kit-kinase induces a cascade of protein tyrosine phosphorylation in normal human melanocytes in response to mast cell growth factor and stimulates mitogen-activated protein kinase but is down-regulated in melanomas.
AU Funasaka Y; Boulton T; Cobb M; Yarden Y; Fan B; Lyman S D; Williams D E; Anderson D M; Zakut R; Mishima Y; et al
CS Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut 06510.
NC 1RO1-AR39848 (NIAMS)
5-R29-CA44542 (NCI)
DK 34128 (NIDDK)
SO MOLECULAR BIOLOGY OF THE CELL, **(1992 Feb)** 3 (2) 197-209.
Journal code: BAU. ISSN: 1059-1524.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199207
AB The proto-oncogene c-Kit, a transmembrane receptor tyrosine kinase, is an important regulator of cell growth whose constitutively active oncogenic counterpart, v-kit, induces sarcomas in cats. Mutations in murine c-kit that reduce the receptor tyrosine kinase activity cause deficiencies in the migration and proliferation of melanoblasts, hematopoietic stem cells, and primordial germ cells. We therefore investigated whether c-Kit regulates normal human melanocyte proliferation and plays a role in melanomas. We show that normal human melanocytes respond to mast cell growth factor (MGF), the Kit-ligand that stimulates phosphorylation of tyrosyl residues in c-Kit and induces sequential phosphorylation of tyrosyl residues in several other proteins. One of the phosphorylated intermediates in the signal transduction pathway was identified as an early response kinase (mitogen-activated protein [MAP] kinase). Dephosphorylation of a prominent 180-kDa protein suggests that MGF also activates a phosphotyrosine phosphatase. In contrast, MGF did not induce proliferation, the cascade of protein phosphorylations, or MAP kinase activation in the majority of cells cultured from primary nodular and metastatic melanomas that grow independently of exogenous factors. In the five out of eight human melanoma lines expressing c-kit mRNAs, c-Kit was not constitutively activated. Therefore, although c-Kit-kinase is a potent growth regulator of normal human melanocytes, its activity is not positively associated with malignant transformation.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Cells, Cultured
Enzyme Activation: PH, physiology
Gene Expression Regulation, Enzymologic
Gene Expression Regulation, Neoplastic
*Interleukin-3: PH, physiology
***Melanocytes: EN, enzymology**

*Melanoma: EN, enzymology
Phosphorylation
***Protein Kinases: PH, physiology**
Protein-Tyrosine Kinase: PH, physiology
*Proto-Oncogene Proteins: PH, physiology
Signal Transduction: PH, physiology
Tumor Cells, Cultured
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.37 (Protein Kinases); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Interleukin-3); 0 (Proto-Oncogene Proteins)

L42 ANSWER 104 OF 109 MEDLINE
AN 92084100 MEDLINE
DN 92084100
TI Ectopic expression of a c-kitW42 minigene in transgenic mice: recapitulation of W phenotypes and evidence for c-kit function in melanoblast progenitors.
AU Ray P; Higgins K M; Tan J C; Chu T Y; Yee N S; Nguyen H; Lacy E; Besmer P
CS Molecular Biology Program, Sloan Kettering Institute, New York, New York.
SO GENES AND DEVELOPMENT, **(1991 Dec)** 5 (12A) 2265-73.
Journal code: FN3. ISSN: 0890-9369.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199203
AB The proto-oncogene c-kit encodes a transmembrane tyrosine kinase receptor that is allelic with the murine white-spotting locus (W). W mutations affect melanogenesis, gametogenesis, and hematopoiesis during development and adult life, and they result from the partial or complete loss of c-kit function. The W42 allele is a W mutation with severe effects in both the homozygous and the heterozygous states. Previous analysis of the W42 allele identified a missense mutation in an essential amino acid of the c-kitW42 kinase domain that abolishes the in vitro kinase activity of the c-kitW42 protein but does not affect its normal expression. These results suggested that the c-kitW42 allele was a dominant negative mutation within the context of c-kit-mediated signal transduction. To further explore the dominant negative characteristics of the W42 mutation, we have generated transgenic mice in which ectopic expression is driven by the human beta-actin promoter (hAP). Two mouse lines carrying the hAP-c-kitW42 transgene show an effect on pigmentation and the number of tissue mast cells. The patchy coat color pattern of the line 695 mice may reflect variable expression of the transgene in melanoblast progenitors and their descendants and, consequently, is indicative of a function for c-kit in early melanoblasts. Germ cell development and erythropoiesis, however, do not appear to be affected by the transgene. Mice expressing the c-kitW42 transgene therefore recapitulate some of the phenotypes of mice with W mutations. These results are therefore in agreement with the molecular basis of the W42 mutation and the dominant-negative characteristics of the c-kitW42 protein product.
CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alleles
Gametogenesis
***Hair Color: GE, genetics**
Hematopoiesis
Mast Cells: CY, cytology
***Melanocytes: CY, cytology**
Mice
Mice, Inbred CBA
Mice, Inbred C57BL
Mice, Transgenic
Mutation
Pedigree
Phenotype
***Protein-Tyrosine Kinase: GE, genetics**

*Proto-Oncogene Proteins: GE, genetics
***Receptors, Cell Surface: GE, genetics**
RNA, Messenger: ME, metabolism
Stem Cells: CY, cytology
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface); 0 (RNA, Messenger)

L42 ANSWER 105 OF 109 MEDLINE
AN 92073391 MEDLINE
DN 92073391
TI Deletion of the c-kit protooncogene in the human developmental defect piebald trait.
AU Fleischman R A; Saltman D L; Stastny V; Zneimer S
CS Department of Medicine, University of Texas Southwestern Medical Center, Dallas 75235.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1991 Dec 1)** 88 (23) 10885-9.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199203
AB The protooncogene c-kit is critical for development of hematopoietic stem cells, germ cells, and melanoblasts in the mouse. Homozygous mutations of this gene in the mouse cause anemia, infertility, and albinism, whereas heterozygous mutant mice usually exhibit only a white forehead blaze and depigmentation of the ventral body, tail, and feet. The heterozygous mouse phenotype is very similar to human piebald trait, which is characterized by a congenital white hair forelock and ventral and extremity depigmentation. To investigate the possibility that alterations in the human c-kit gene may be a cause of piebald trait, DNA from seven unrelated affected individuals was examined by Southern blot analysis. One subject, although cytogenetically normal, has a heterozygous deletion of the c-kit protooncogene. This deletion encompasses the entire coding region for c-kit and also involves the closely linked gene for platelet-derived growth factor receptor alpha. Fluorescence in situ hybridization of genomic c-kit probes to metaphase chromosomes independently confirmed the deletion in this case. These findings provide molecular evidence mapping piebald trait to the c-kit locus on chromosome 4. Although we cannot exclude the involvement of other closely linked genes, the demonstration of a genomic c-kit deletion in one subject with piebald trait and the marked concordance of the human and mouse phenotypes provide strong evidence for the role of c-kit in the development of human melanocytes and in the pathogenesis of piebald trait.
CT Check Tags: Animal; Case Report; Female; Human; Male; Support, Non-U.S. Gov't
Blotting, Southern
*Chromosome Deletion
*Chromosomes, Human, Pair 4
DNA: GE, genetics
DNA: IP, isolation & purification
Genotype
Growth Substances: GE, genetics
Heterozygote Detection
Interleukin-2: GE, genetics
Mice
Mice, Inbred C3H
Neoplasm Proteins: GE, genetics
Nucleic Acid Hybridization
***Piebaldism: GE, genetics**
Platelet-Derived Growth Factor: ME, metabolism
Protein-Tyrosine Kinase: GE, genetics
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes

Receptors, Cell Surface: GE, genetics
Restriction Mapping
RN 9007-49-2 (DNA)
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; EC 2.7.11.- (Receptors, Platelet-Derived Growth Factor); 0 (melanoma growth stimulatory activity); 0 (Growth Substances); 0 (Interleukin-2); 0 (Neoplasm Proteins); 0 (Platelet-Derived Growth Factor); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface)
GEN c-kit

L42 ANSWER 106 OF 109 MEDLINE
AN 92020918 MEDLINE
DN 92020918
TI Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism.
AU Giebel L B; Spritz R A
CS Department of Medical Genetics, University of Wisconsin, Madison 53706.
NC AR-39892 (NIAMS)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1991 Oct 1)** 88 (19) 8696-9.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-S58145; GENBANK-S58152; GENBANK-X59603; GENBANK-S57442; GENBANK-S57444; GENBANK-S57448; GENBANK-S57457; GENBANK-S57504; GENBANK-S57506; GENBANK-S57596
EM 199201
AB Piebaldism is an autosomal dominant genetic disorder characterized by cogenital patches of skin and hair from which melanocytes are completely absent. A similar disorder of mouse, dominant white spotting (W), results from mutations of the c-Kit protooncogene, which encodes and receptor for mast/stem cell growth factor. We identified a KIT gene mutation in a proband with classic autosomal dominant piebaldism. This mutation results in a Gly----Arg substitution at codon 664, within the tyrosine kinase domain. This substitution was not seen in any normal individuals and was completely linked to the piebald phenotype in the proband's family. Piebaldism in this family thus appears to be the human homologue to dominant white spotting (W) of the mouse.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Base Sequence
DNA Mutational Analysis
Genes, Dominant
Linkage (Genetics)
Molecular Sequence Data
Oligonucleotides: CH, chemistry
Pedigree
***Piebaldism: GE, genetics**
Polymerase Chain Reaction
Polymorphism, Restriction Fragment Length
***Protein-Tyrosine Kinase: GE, genetics**
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
***Receptors, Cell Surface: GE, genetics**
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Oligonucleotides); 0 (Proto-Oncogene Proteins); 0 (Receptors, Cell Surface)

L42 ANSWER 107 OF 109 MEDLINE
AN 91293084 MEDLINE
DN 91293084
TI In utero manipulation of coat color formation by a monoclonal anti-c-kit antibody: two distinct waves of c-kit-dependency during melanocyte development.

AU Nishikawa S; Kusakabe M; Yoshinaga K; Ogawa M; Hayashi S; Kunisada T; Era T; Sakakura T; Nishikawa S
CS Department of Pathology, Kumamoto University Medical School, Japan.
SO EMBO JOURNAL, **(1991 Aug)** 10 (8) 2111-8.
Journal code: EMB. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
AB Previous studies on mice bearing various mutations within the c-kit gene, dominant white spotting (W), indicate the functional role of this tyrosine kinase receptor in the development of melanocytes, germ cells and hematopoietic cells. Despite the availability of mice defective in the c-kit gene and a respectable understanding of the molecular nature of c-kit, however, it is not clear at what stage of gestation c-kit is functionally required for the development of each of these cell lineages. To address this question, we have used a monoclonal anti-c-kit antibody, ACK2, as an antagonistic blocker of c-kit function to interfere with the development of melanocytes during embryonic and postnatal life. ACK2 injected intradermally into pregnant mice entered the embryos where it blocked the proper development of melanocytes. This inhibitory effect was manifested as coat color alteration in the offspring. Furthermore, ACK2 injection also altered the coat color of neonatal and adult mice. Based on the coat color patterns produced by ACK2 administration at various stages before or after birth, the following conclusions are drawn: (i) during mid-gestation, c-kit is functionally required during a restricted period around day 14.5 post-coitum when a sequence of events leading to melanocyte entry into the epidermal layer occurs; (ii) during postnatal life, c-kit is required for melanocyte activation which occurs concomitantly with the hair cycle which continues throughout life after neonatal development of the first hair.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*Antibodies, Monoclonal: IM, immunology
***Hair Color**
Immunohistochemistry
Mast Cells
***Melanocytes: CY, cytology**
Melanocytes: PH, physiology
Mice
Mice, Inbred C57BL
Pregnancy
Protein-Tyrosine Kinase: IM, immunology
***Protein-Tyrosine Kinase: PH, physiology**
Proto-Oncogene Proteins: IM, immunology
*Proto-Oncogene Proteins: PH, physiology
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Antibodies, Monoclonal); 0 (Proto-Oncogene Proteins)
GEN c-kit

L42 ANSWER 108 OF 109 MEDLINE
AN 91277602 MEDLINE
DN 91277602
TI The rat c-kit ligand, stem cell factor, induces the development of connective tissue-type and mucosal mast cells in vivo. Analysis by anatomical distribution, histochemistry, and protease phenotype.
AU Tsai M; Shih L S; Newlands G F; Takeishi T; Langley K E; Zsebo K M; Miller H R; Geissler E N; Galli S J
CS Department of Pathology, Beth Israel Hospital, Boston, Massachusetts 02215.
NC AI-22674 (NIAID)
AI-23990 (NIAID)
CA-28834 (NCI)
+
SO JOURNAL OF EXPERIMENTAL MEDICINE, **(1991 Jul 1)** 174 (1) 125-31.

Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199110
AB Mast cell development is a complex process that results in the appearance of phenotypically distinct populations of mast cells in different anatomical sites. Mice homozygous for mutations at the W or S1 locus exhibit several phenotypic abnormalities, including a virtual absence of mast cells in all organs and tissues. Recent work indicates that W encodes the c-kit tyrosine kinase receptor, whereas S1 encodes a c-kit ligand that we have designated stem cell factor (SCF). Recombinant or purified natural forms of the c-kit ligand induce proliferation of certain mast cell populations in vitro, and injection of recombinant SCF permits mast cells to develop in mast cell-deficient WCB6F1-S1/S1d mice. However, the effects of SCF on mast cell proliferation, maturation, and phenotype in normal mice in vivo were not investigated. We now report that local administration of SCF in vivo promotes the development of connective tissue-type mast cells (CTMC) in the skin of mice and that systemic administration of SCF induces the development of both CTMC and mucosal mast cells (MMC) in rats. Rats treated with SCF also develop significantly increased tissue levels of specific rat mast cell proteases (RMCP) characteristic of either CTMC (RMCP I) or MMC (RMCP II). These findings demonstrate that SCF can induce the expansion of both CTMC and MMC populations in vivo and show that SCF can regulate at least one cellular lineage that expresses c-kit, the mast cell, through complex effects on proliferation and maturation.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Division
*Connective Tissue: CY, cytology
***Endopeptidases: ME, metabolism**
Genotype
*Hematopoietic Cell Growth Factors: PD, pharmacology
Homozygote
*Mast Cells: CY, cytology
Mast Cells: DE, drug effects
Mast Cells: EN, enzymology
Mice
Mice, Mutant Strains
Mucous Membrane: CY, cytology
Organ Specificity
Rats
Rats, Inbred Strains
Recombinant Proteins: PD, pharmacology
***Skin: CY, cytology**
Skin: DE, drug effects
CN EC 3.4.- (Endopeptidases); 0 (Hematopoietic Cell Growth Factors); 0 (Recombinant Proteins); **0 (Stem Cell Factor)**

L42 ANSWER 109 OF 109 MEDLINE
AN 89306618 MEDLINE
DN 89306618
TI Expression of c-kit gene products in known cellular targets of W mutations in normal and W mutant mice--evidence for an impaired c-kit kinase in mutant mice.
AU Nocka K; Majumder S; Chabot B; Ray P; Cervone M; Bernstein A; Besmer P
CS Molecular Biology Program, Sloan Kettering Institute, New York, New York.
NC CA-32926 (NCI)
SO GENES AND DEVELOPMENT, **(1989 Jun)** 3 (6) 816-26.
Journal code: FN3. ISSN: 0890-9369.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 198910
AB The proto-oncogene c-kit, a transmembrane tyrosine protein kinase receptor for an unknown ligand, was shown recently to map to the dominant white spotting locus (W) of the mouse. Mutations at the W locus affect various aspects of hematopoiesis, as well as the proliferation and/or migration of primordial germ cells and melanoblasts during development. Here, we show that c-kit is expressed in tissues known to be affected by W mutations in fetal and adult erythropoietic tissues, mast cells, and neural-crest-derived melanocytes. We demonstrate that the c-kit associated tyrosine-specific protein kinase is functionally impaired in W/WV mast cells, thus providing a molecular basis for understanding the developmental defects that result from these mutations.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alleles
Anemia, Macrocytic: EN, enzymology
*Anemia, Macrocytic: GE, genetics
Cell Movement
Fetal Development
Genes, Lethal
Hematopoiesis
Hematopoietic Stem Cells: EN, enzymology
Heterozygote
Liver: EM, embryology
Liver: EN, enzymology
Mast Cells: EN, enzymology
Melanocytes: EN, enzymology
Melanoma, Experimental
Mice
Mice, Mutant Strains: EM, embryology
*Mice, Mutant Strains: GE, genetics
Mice, Mutant Strains: ME, metabolism
Neural Crest: PA, pathology
Organ Specificity
Pigmentation Disorders: EM, embryology
Pigmentation Disorders: EN, enzymology
***Pigmentation Disorders: GE, genetics**
Protein-Tyrosine Kinase: DF, deficiency
***Protein-Tyrosine Kinase: GE, genetics**
Proto-Oncogene Proteins: BI, biosynthesis
*Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogenes
RNA, Messenger: AN, analysis
Tumor Cells, Cultured: EN, enzymology
CN EC 2.7.1.112 (Protein-Tyrosine Kinase); **EC 2.7.11.- (Proto-Oncogene Protein c-kit)**; 0 (Proto-Oncogene Proteins); 0 (RNA, Messenger)

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L55         105 S L44 AND ?PIGMENT?
L56          81 S L55 AND L45
L57          74 S L56 NOT LONGLEY B?/AU
L58          70 S L56 NOT L54
L59          12 S L58 AND (LIGAND OR UVB OR PIEBALDISM)/TI
L60          93 S L54,L59,L57
L61          23 S L60 AND 00520/CC
L62          22 S L60 AND CONFERENCE/DT
L63          70 S L60 NOT L61,L62
L64           1 S L63 AND SEMINAR/SO
L65          24 S L61,L62,L64
L66          69 S L60 NOT L65

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L65  ANSWER 1 OF 24  BIOSIS  COPYRIGHT 2001 BIOSIS
AN   2000:87137  BIOSIS
DN   PREV200000087137
TI   The paracrine mechanism of accentuated epidermal pigmentation in
     dermatofibroma: Role of fibroblast-derived melanogenic cytokines.
AU   Kurishima, Etsuko (1); Manaka, Izumi; Kadono, Satsuki; Kawashima, Makoto;
     Imokawa, Genji
CS   (1) Tokyo Women's Medical University, Tokyo, 162-8666 Japan
SO   Pigment Cell Research, (1999) No. SUPPL. 7, pp. 80.
     Meeting Info.: XVIIth International Pigment Cell Conference Nagoya, Japan
     October 30-November 3, 1999
     ISSN: 0893-5785.
DT   Conference
LA   English
CC   Neoplasms and Neoplastic Agents - General  *24002
     Cytology and Cytochemistry - Animal  *02506
     Genetics and Cytogenetics - Animal  *03506
     Biochemical Studies - General  *10060
     Integumentary System - General; Methods  *18501
     Endocrine System - General  *17002
     General Biology - Symposia, Transactions and Proceedings of
     Conferences, Congresses, Review Annuals  *00520
BC   Animalia - Unspecified  33000
IT   Major Concepts
        Integumentary System (Chemical Coordination and Homeostasis); Tumor
        Biology
IT   Parts, Structures, & Systems of Organisms
        epidermis: integumentary system; mast cells: immune system;
        melanocytes: integumentary system
IT   Diseases
        dermatofibroma: integumentary system disease, neoplastic disease
IT   Chemicals & Biochemicals
        hepatocyte growth factor; mRNA [messenger RNA]; stem
      cell factor
IT   Alternate Indexing
        Dermatofibroma (MeSH)
IT   Miscellaneous Descriptors
        hyperpigmentation; Meeting Abstract; Meeting Poster
ORGN Super Taxa
        Animalia
ORGN Organism Name
        animal (Animalia)
ORGN Organism Superterms
        Animals

L65  ANSWER 2 OF 24  BIOSIS  COPYRIGHT 2001 BIOSIS
AN   2000:83938  BIOSIS
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DN PREV200000083938
TI Role of keratinocyte-derived cytokines and their receptors in **hypopigmentation** in vitiligo vulgaris.
AU Kitamura, Reiko (1); Tsukamoto, Katsuhiko (1); Shimada, Shinji (1); Imokawa, Genji
CS (1) Department of Dermatology, Yamanashi Medical University, Yamanashi, 409-3898 Japan
SO Pigment Cell Research, (1999) No. SUPPL. 7, pp. 86.
Meeting Info.: XVIIth International Pigment Cell Conference Nagoya, Japan October 30-November 3, 1999
ISSN: 0893-5785.
DT **Conference**
LA English
CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Endocrine System - General *17002
Integumentary System - Pathology *18506
Immunology and Immunochemistry - General; Methods *34502
Integumentary System - Physiology and Biochemistry *18504
Biophysics - General Biophysical Studies *10502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Cell Biology; Integumentary System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
epidermis: integumentary system, lesional, non-lesional; melanocytes: cytokine receptor expression, integumentary system, melanogenic function, regulation
IT Diseases
vitiligo vulgaris: integumentary system disease, pathogenesis
IT Chemicals & Biochemicals
ET-1 [endothelin-1]: epidermal expression; ET-B receptor [endothelin-B receptor]: epidermal expression; GM-CSF [granulocyte-macrophage colony stimulating factor]: epidermal expression; SCF [**stem cell factor**]: epidermal expression; **c-Kit**: epidermal expression; cytokine: keratinocyte-derived, regulatory, secretion
IT Methods & Equipment
immunohistochemistry: histochemical method; immunostaining: analytical method; reverse transcription polymerase chain reaction: analytical method
IT Miscellaneous Descriptors
hypopigmentation; Meeting Abstract; Meeting Poster
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 76543-79-8 (ET-1)
123626-67-5 (ENDOTHELIN-1)
83869-56-1 (GM-CSF)
83869-56-1 (GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR)

L65 ANSWER 3 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:83864 BIOSIS
DN PREV200000083864
TI A paracrine role of **stem cell factor/ c-kit** linkage in **UVB**-induced **pigmentation**.
AU Hachiya, Akira (1); Kobayashi, Akemi (1); Ohuchi, Atushi (1); Takema, Yoshinori (1); Imokawa, Genji (1)
CS (1) Biological Science Laboratories, Kao Corporation, Ichikaimachi, Tochigi, 321-3497 Japan

SO Pigment Cell Research, (1999) No. SUPPL. 7, pp. 45.
Meeting Info.: XVIIth International Pigment Cell Conference Nagoya, Japan October 30-November 3, 1999
ISSN: 0893-5785.
DT **Conference**
LA English
CC **Integumentary System - Physiology and Biochemistry *18504**
Cytology and Cytochemistry - Human *02508
Radiation - Radiation Effects and Protective Measures *06506
Endocrine System - General *17002
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
BC Hominidae 86215
IT Major Concepts
Integumentary System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
keratinocytes: integumentary system; melanocytes: integumentary system
IT Chemicals & Biochemicals
c-Kit; stem cell factor
IT Miscellaneous Descriptors
UV B; **pigmentation**; Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L65 ANSWER 4 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:127781 BIOSIS
DN PREV199900127781
TI The Asp816Val **C-kit** mutation is present in the peripheral blood of adult patients with urticaria **pigmentosa**.
AU Akin, C.; Kirshenbaum, A.; Scott, L. M.; Semere, T.; Metcalfe, D. D.
CS Lab. Allergic Dis., NIAID, NIH, Bethesda, MD USA
SO Journal of Allergy and Clinical Immunology, (**Jan., 1999**) Vol. 103, No. 1 PART 2, pp. S233.
Meeting Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999
American Academy of Allergy, Asthma, and Immunology
. ISSN: 0091-6749.
DT **Conference**
LA English
CC Genetics and Cytogenetics - Human *03508
Blood, Blood-Forming Organs and Body Fluids - General; Methods *15001
Integumentary System - General; Methods *18501
Immunology and Immunochemistry - General; Methods *34502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Dermatology (Human Medicine, Medical Sciences); Medical Genetics (Allied Medical Sciences)
IT Parts, Structures, & Systems of Organisms
peripheral blood
IT Diseases
mastocytosis: congenital disease, integumentary system disease; urticaria **pigmentosa**: congenital disease, integumentary system disease
IT Alternate Indexing
Mastocytosis (MeSH); Urticaria **Pigmentosa** (MeSH)
IT Miscellaneous Descriptors
pathogenesis; Asp816Val **C-kit** mutation; Meeting Abstract
ORGN Super Taxa

Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): adult, patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L65 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:292932 BIOSIS
DN PREV199800292932
TI Rapid reduction in the size of mouse cutaneous mast cell populations by apoptosis after cessation of treatment with SCF does not result in skin **inflammation**.
AU Maurer, Marcus (1); Galli, Stephen J.
CS (1) Dep. Pathology, Beth Israel Deaconess Med. Cent., Boston, MA USA
SO Journal of Dermatological Science, (**March, 1998**) Vol. 16, No. SUPPL. 1, pp. S162.
Meeting Info.: Third Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology, Society for Investigative Dermatology Cologne, Germany May 7-10, 1998 European Society for Dermatological Research
. ISSN: 0923-1811.
DT **Conference**
LA English
CC Immunology and Immunochemistry - General; Methods *34502
Genetics and Cytogenetics - Animal *03506
Integumentary System - General; Methods *18501
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Muridae 86375
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
cutaneous mast cells: immune system
IT Chemicals & Biochemicals
SCF [**stem cell factor**]
IT Miscellaneous Descriptors
apoptosis; skin **inflammation**; Meeting Abstract
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L65 ANSWER 6 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:248327 BIOSIS
DN PREV199800248327
TI Rapid reduction in the size of mouse cutaneous mast cell populations by apoptosis after cessation of treatment with SCF does not result in skin **inflammation**.
AU Maurer, Marcus (1); Galli, Stephen J.
CS (1) Dep. Pathol., Beth Israel Deaconess Med. Cent., Boston, MA USA
SO Journal of Investigative Dermatology, (**April, 1998**) Vol. 110, No. 4, pp. 634.
Meeting Info.: Annual Meeting of the International Investigative Dermatology Cologne, Germany May 7-10, 1998 The Society for Investigative Dermatology, Inc.
. ISSN: 0022-202X.
DT **Conference**
LA English
CC **Integumentary System - Pathology *18506**
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Immunology and Immunochemistry - Immunopathology, Tissue Immunology

*34508
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Muridae 86375
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
mast cell: immune system; skin: integumentary system
IT Chemicals & Biochemicals
stem cell factor
IT Miscellaneous Descriptors
apoptosis; **inflammation**; Meeting Abstract; Meeting Poster
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L65 ANSWER 7 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:331763 BIOSIS
DN PREV199799630966
TI The comparative molecular biology, genetics and evolution of axolotl **pigment** cells.
AU Mason, Kenneth A.
CS Dep. Biochemistry Cell. Mol. Biol., Univ. Kansas, Lawrence, KS 66045 USA
SO Pigment Cell Research, (1997) Vol. 10, No. 1-2, pp. 114.
Meeting Info.: XVIth International Pigment Cell Conference Anaheim, California, USA October 29-November 1, 1996
ISSN: 0893-5785.
DT **Conference**; Abstract
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - General *10060
Enzymes - General and Comparative Studies; Coenzymes *10802
Integumentary System - General; Methods *18501
BC Vertebrata - Unspecified 85150
Caudata *85304
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Integumentary System (Chemical Coordination and Homeostasis)
IT Chemicals & Biochemicals
TYROSINASE; ALDEHYDE OXIDASE; TYROSINE KINASE
IT Miscellaneous Descriptors
ALDEHYDE OXIDASE; **C-KIT** RECEPTO TYROSINE KINASE; CDNA; COMPARATIVE GENETICS; COMPARATIVE MOLECULAR BIOLOGY; COMPLEMENTARY DNA; EMBRYO; INTEGUMENTARY SYSTEM; MOLYBDOPTERIN-BINDING PROTEINS; MUTATION; **PIGMENT** CELL DIFFERENTIATION; **PIGMENT** CELL EVOLUTION; TRP-1; TYROSINASE GENE FAMILY; XDH
ORGN Super Taxa
Caudata: Amphibia, Vertebrata, Chordata, Animalia; Vertebrata - Unspecified: Vertebrata, Chordata, Animalia
ORGN Organism Name
axolotl (Caudata); vertebrates (Vertebrata - Unspecified); Vertebrata (Vertebrata - Unspecified)
ORGN Organism Superterms
amphibians; animals; chordates; nonhuman vertebrates; vertebrates
RN 9002-10-2 (TYROSINASE)
9029-07-6 (ALDEHYDE OXIDASE)
80449-02-1 (TYROSINE KINASE)

L65 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:101845 BIOSIS
DN PREV199799401048
TI Growth and motility of melanocytes caused by targeting expression of SCF to the skin.
AU Kunisada, Takahiro (1); Nishikawa, Shin-Ichi; Nishikawa, Satomi; Yoshida, Hisahiro; Mizoguchi, Masako; Hayashi, Shin-Ichi
CS (1) Dep. Immunol., Fac. Med., Tottori Univ., Yonago 683 Japan
SO Pigment Cell Research, (1996) Vol. 9, No. 4, pp. 172.
Meeting Info.: 11th Annual Meeting of the Japanese Society for Pigment Cell Research Kawasaki, Japan December 6-7, 1996
ISSN: 0893-5785.
DT **Conference**; Abstract
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Movement *12100
Metabolism - Proteins, Peptides and Amino Acids *13012
Endocrine System - General *17002
Integumentary System - Physiology and Biochemistry *18504
Developmental Biology - Embryology - Morphogenesis, General *25508
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Integumentary System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Metabolism; Physiology
IT Chemicals & Biochemicals
TYROSINE KINASE
IT Miscellaneous Descriptors
C-KIT RECEPTOR TYROSINE KINASE; **C-KIT** RECEPTOR TYROSINE KINASE LIGAND; DEVELOPMENT; ENDOCRINE SYSTEM; INTEGUMENTARY SYSTEM; MELANOCYTE DIFFERENTIATION; MELANOCYTE GROWTH; MELANOCYTE MOTILITY; MELANOCYTE PROLIFERATION; MELANOCYTES; NEWBORN; **PIGMENT** CELL; SCF; SKIN; **STEM CELL FACTOR**; TARGETING EXPRESSION; TRANSGENIC
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 80449-02-1 (TYROSINE KINASE)

L65 ANSWER 9 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:101844 BIOSIS
DN PREV199799401047
TI Differentiation, proliferation and survival of mouse melanoblast cells in distinct developmental stage.
AU Yoshida, Hisahiro; Nishikawa, Shin-Ichi
CS Dep. Molecular Genetics, Fac. Med., Kyoto Univ., Kyoto 606-01 Japan
SO Pigment Cell Research, (1996) Vol. 9, No. 4, pp. 171.
Meeting Info.: 11th Annual Meeting of the Japanese Society for Pigment Cell Research Kawasaki, Japan December 6-7, 1996
ISSN: 0893-5785.
DT **Conference**; Abstract
LA English

CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Metabolism - Proteins, Peptides and Amino Acids *13012
Cardiovascular System - Physiology and Biochemistry *14504
Endocrine System - General *17002
Endocrine System - Neuroendocrinology *17020
Integumentary System - Anatomy *18502
Integumentary System - Physiology and Biochemistry *18504
Nervous System - Physiology and Biochemistry *20504
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Morphogenesis, General *25508
In Vitro Studies, Cellular and Subcellular *32600
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cardiovascular System (Transport and Circulation); Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Nervous System (Neural Coordination)
IT Miscellaneous Descriptors
ANALYTICAL METHOD; CELL CULTURE; DEVELOPMENT; DISTINCT DEVELOPMENTAL STAGE; EMBRYO; EMBRYOGENESIS; ENDOTHELIN; IN-VITRO; INTEGUMENTARY SYSTEM; MELANOBLAST CELL DIFFERENTIATION; MELANOBLAST CELL PROLIFERATION; MELANOBLAST CELL SURVIVAL; MELANOBLAST CELLS; MELANOBLAST DEVELOPMENT; MORPHOLOGY; **PIGMENT** CELL; SCF; SKIN; **STEM CELL FACTOR**
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

L65 ANSWER 10 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:101843 BIOSIS
DN PREV199799401046
TI Induction of melanocytes from cultured mouse neural crest cells by TPA and endothelin depends on intrinsic SCF from the explants.
AU Ono, Hirotake (1); Kawa, Yoko; Asano, Mari; Kubota, Yasuo; Matsumoto, Jiro; Mizoguchi, Masako
CS (1) Dep. Biol., Keio Univ., Yokohama 223 Japan
SO Pigment Cell Research, (1996) Vol. 9, No. 4, pp. 171.
Meeting Info.: 11th Annual Meeting of the Japanese Society for Pigment Cell Research Kawasaki, Japan December 6-7, 1996
ISSN: 0893-5785.
DT **Conference**; Abstract
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Anatomy and Histology, General and Comparative - Experimental Anatomy *11104
Metabolism - Proteins, Peptides and Amino Acids *13012
Cardiovascular System - Physiology and Biochemistry *14504
Cardiovascular System - Blood Vessel Pathology *14508
Endocrine System - General *17002
Endocrine System - Neuroendocrinology *17020
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Physiology and Biochemistry *18504

Integumentary System - Pathology *18506
Nervous System - Physiology and Biochemistry *20504
Nervous System - Pathology *20506
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Experimental *25504
Developmental Biology - Embryology - Morphogenesis, General *25508
Developmental Biology - Embryology - Descriptive Teratology and Teratogenesis *25552
In Vitro Studies, Cellular and Subcellular *32600
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cardiovascular System (Transport and Circulation); Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Morphology; Nervous System (Neural Coordination); Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
ANALYTICAL METHOD; **C-KIT**; CELL CULTURE; DEPOSITION; DEVELOPMENT; EMBRYO; ENDOCRINE SYSTEM; ENDOTHELIN; EXPLANTS; IN-VITRO; INTEGUMENTARY SYSTEM; INTRINSIC SCF; INTRINSIC **STEM CELL FACTOR**; MELANIN; MELANOCYTE DIFFERENTIATION; MELANOCYTE INDUCTION; MELANOCYTES; NEURAL CREST CELL DEVELOPMENT; **PIGMENT** CELL; SIGNAL TRANSDUCTION; SURGICAL METHOD; TPA
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

L65 ANSWER 11 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:101842 BIOSIS
DN PREV199799401045
TI Signaling mechanisms of MAP kinase activation induced by ET-1 in NHMC.
AU Miyagishi, Makoto; Kobayashi, Takeshi; Imokawa, Genji
CS Biological Sci. Lab., Kao Corporation, Haga, Tochigi 321-34 Japan
SO Pigment Cell Research, (1996) Vol. 9, No. 4, pp. 171.
Meeting Info.: 11th Annual Meeting of the Japanese Society for Pigment Cell Research Kawasaki, Japan December 6-7, 1996
ISSN: 0893-5785.
DT **Conference**; Abstract
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Cardiovascular System - Physiology and Biochemistry *14504
Endocrine System - General *17002
Endocrine System - Neuroendocrinology *17020
Integumentary System - Physiology and Biochemistry *18504
Nervous System - Physiology and Biochemistry *20504
In Vitro Studies, Cellular and Subcellular *32600
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cardiovascular System (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Nervous System (Neural Coordination)
IT Chemicals & Biochemicals

KINASE; ET-1; PROTEIN KINASE
IT Miscellaneous Descriptors
ACTIVATION; ACTIVITY; ANALYTICAL METHOD; CELL CULTURE; DNA; ENDOCRINE SYSTEM; ENDOTHELIN-1; ENZYMOLOGY; ET-1; INTEGUMENTARY SYSTEM; MAPK; MITOGEN; MITOGEN-ACTIVATED PROTEIN KINASE; NHMC; NORMAL HUMAN MELANOCYTES; PHOSPHORYLATION; **PIGMENT** CELL; RAF-1; SIGNAL TRANSDUCTION PATHWAYS; SIGNALING MECHANISMS; **STEM CELL FACTOR**; SYNTHESIS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 9031-44-1 (KINASE)
76543-79-8 (ET-1)
9026-43-1 (PROTEIN KINASE)

L65 ANSWER 12 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:101813 BIOSIS
DN PREV199799401016
TI Segregation of melanocyte precursors and regulation of their fate during neural crest development.
AU Weston, James A.; Wehrle-Haller, Bernard
CS Inst. Neuroscience, Univ. Oregon, Eugene, OR 97403-1254 USA
SO Pigment Cell Research, (1996) Vol. 9, No. 4, pp. 164.
Meeting Info.: 11th Annual Meeting of the Japanese Society for Pigment Cell Research Kawasaki, Japan December 6-7, 1996
ISSN: 0893-5785.
DT **Conference**; Abstract
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Movement *12100
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Endocrine System - General *17002
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Integumentary System - Physiology and Biochemistry *18504
Nervous System - Physiology and Biochemistry *20504
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Morphogenesis, General *25508
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Metabolism; Nervous System (Neural Coordination); Physiology; Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
STEEL
IT Miscellaneous Descriptors
C-KIT; DEVELOPMENT; EMBRYO; INTEGUMENTARY SYSTEM; MELANOCYTE PRECURSOR FATE REGULATION; MELANOCYTE PRECURSOR SEGREGATION; MELANOCYTE PRECURSORS; MIGRATION STAGING AREA; NEURAL CREST DEVELOPMENT; NEURAL CREST MIGRATION PATHWAY; **PIGMENT** CELL; SKIN; STEEL FACTOR; STEEL FACTOR MESSENGER RNA; STEEL FACTOR MRNA; STEEL FACTOR RECEPTOR; STEEL FACTOR RECEPTOR MESSENGER RNA; STEEL FACTOR RECEPTOR MRNA
ORGN Super Taxa

Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Vertebrata - Unspecified: Vertebrata, Chordata, Animalia
ORGN Organism Name
murine (Muridae); vertebrate (Vertebrata - Unspecified)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 12597-69-2 (STEEL)

L65 ANSWER 13 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:550616 BIOSIS
DN PREV199699272972
TI Characterization of keratinocyte- and fibroblast-derived mitogens for human melanocytes: Their roles in stimulated cutaneous **pigmentation**.
AU Imokawa, Genji (1); Yada, Yukihiro; Morisaki, Naoko; Kimura, Mitsutoshi
CS (1) Inst. Fundamental Res., Kao Corporation, 2602 Akabane, Ichikai-Machi, Haga, Tochigi 321-34 Japan
SO Hori, Y. [Editor]; Hearing, V. J. [Editor]; Nakayama, J. [Editor]. International Congress Series, (1996) No. 1096, pp. 35-48. International Congress Series; Melanogenesis and malignant melanoma: Biochemistry, cell biology, molecular biology, pathophysiology, diagnosis and treatment. Publisher: Elsevier Science Publishers B.V. PO Box 211, Sara Burgerhartstraat 25, 1000 AE Amsterdam, Netherlands.
Meeting Info.: International Symposium on Melanogenesis and Malignant Melanoma Fukuoka, Japan December 4-6, 1995
ISSN: 0531-5131. ISBN: 0-444-82209-7.
DT Book; **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human 02508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Endocrine System - General *17002
Integumentary System - Physiology and Biochemistry *18504
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Metabolism
IT Miscellaneous Descriptors
BOOK CHAPTER; DNA SYNTHESIS; ENDOTHELIN-1; EPIDERMAL MELANOSIS; GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR; INTERLEUKIN-1 ALPHA; MEETING PAPER; **STEM CELL FACTOR**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L65 ANSWER 14 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:248112 BIOSIS
DN PREV199698804241
TI The role of the **c-KIT proto-oncogene** and its **ligand**, mast cell growth factor, in the pathogenesis of mastocytosis.
AU Tyrrell, Lynda (1); Schechter, Norman; Langley, Keith; Longley, B. Jack (1)
CS (1) Dep. Dermatol., Yale Univ. Sch. Med., New Haven, CT USA
SO Journal of Investigative Dermatology, (1996) Vol. 106, No. 4, pp. 819.
Meeting Info.: Annual Meeting of the Society for Investigative Dermatology

Washington, D.C., USA May 1-5, 1996
ISSN: 0022-202X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Endocrine System - General *17002
Integumentary System - Pathology *18506
BC Hominidae *86215
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Dermatology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics
IT Miscellaneous Descriptors
MEETING ABSTRACT; URTICARIA **PIGMENTOSA**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L65 ANSWER 15 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:144931 BIOSIS
DN PREV199698717066
TI Histamine release from human skin mast cells by monocyte chemoattractant factor: 1. RANTES, macrophage **inflammatory** protein - 1-alpha, and **stem cell factor** using microdialysis technique.
AU Petersen, L. J.; Brasso, K.; Pryds, M.; Skov, P. S.
CS Copenhagen Denmark
SO Journal of Allergy and Clinical Immunology, (1996) Vol. 97, No. 1 PART 3, pp. 261.
Meeting Info.: Fifty-second Annual Meeting of the American Academy of Allergy Asthma and Immunology New Orleans, Louisiana, USA March 15-20, 1996
ISSN: 0091-6749.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Clinical Biochemistry; General Methods and Applications *10006
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Integumentary System - Physiology and Biochemistry *18504
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Allergy *35500
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Allergy (Clinical Immunology, Human Medicine, Medical Sciences); Blood and Lymphatics (Transport and Circulation); Cell Biology; Clinical

Chemistry (Allied Medical Sciences); Clinical Immunology (Human Medicine, Medical Sciences); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
HISTAMINE
IT Miscellaneous Descriptors
BASOPHILS; CHEMOKINES; MEETING ABSTRACT
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae); rat (Muridae); Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN 51-45-6 (HISTAMINE)

L65 ANSWER 16 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:43812 BIOSIS
DN PREV199698615947
TI Melanocyte-keratinocyte interactions.
AU Ortonne, J.-P
CS INSERM U.385, Biologie Physiopathologie Peau, Nice France
SO Schmitt, D. [Editor]. (1995) pp. 121-131. INSERM continuing education **seminar**: Biology of the skin. Seminaire d'enseignement INSERM: Biologie de la peau.
Publisher: INSERM (Institut National de la Sante et de la Recherche Medicale) 101, rue de Tolbiac, 75654 Paris Cedex 13, France.
ISBN: 2-85598-642-7.
DT Book
LA French
CC Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General *10060
Anatomy and Histology, General and Comparative - Gross Anatomy *11102
Metabolism - General Metabolism; Metabolic Pathways *13002
Blood, Blood-Forming Organs and Body Fluids - General; Methods *15001
Endocrine System - General *17002
Integumentary System - General; Methods *18501
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Morphology
IT Chemicals & Biochemicals
MELANOTROPIN
IT Miscellaneous Descriptors
BOOK CHAPTER; **C-KIT** LIGAND; CELL DIFFERENTIATION; CELL MIGRATION; CELL PROLIFERATION; CYTOKINE SYNTHESIS; DENDRITE FORMATION; DESCRIPTIVE MORPHOLOGY; ENDOCYTOSIS; ENDOTHELIN RECEPTOR; EXOCYTOSIS; HORMONE; IN VITRO MELANOCYTE FUNCTION MODULATION; INTERLEUKIN; MELANOGENESIS; MELANOSOME TRANSFER; MELANOTROPIN; MEMBRANE FUSION; MITOGEN; NEUROTROPIN; **PIGMENT** CELL; VITAMIN
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); mouse (Muridae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN 9002-79-3 (MELANOTROPIN)

L65 ANSWER 17 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:421590 BIOSIS
DN PREV199598435890
TI Human keratinocytes release mast cell differentiation factors other than **stem cell factor**.
AU Welker, Pia (1); Grabbe, Juergen; Czarnetzki, Beate M.
CS (1) Freie Univ. Berlin, Rudolf Virchow Clin. Dermatol., Augustenburger-Platz 1, D-13344 Berlin Germany
SO International Archives of Allergy and Immunology, (1995) Vol. 107, No. 1-3, pp. 139-141.
Meeting Info.: 20th Symposium of the Collegium Internationale Allergologicum on Molecular and Clinical Implications for Allergy in the 21st Century Nantucket, Massachusetts, USA September 25-29, 1994
ISSN: 1018-2438.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies 15004
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Bones, Joints, Fasciae, Connective and Adipose Tissue - Anatomy *18002
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Integumentary System - Anatomy *18502
Integumentary System - Physiology and Biochemistry *18504
Developmental Biology - Embryology - Morphogenesis, General *25508
Tissue Culture, Apparatus, Methods and Media 32500
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Immune System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Pathology; Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
HISTAMINE; TRYPTASE
IT Miscellaneous Descriptors
FIBROBLAST; HISTAMINE; HUMAN HACAT KERATINOCYTE CELL LINE; HUMAN HMC-1 MAST CELL LINE; MEETING ABSTRACT; MEETING PAPER; TRYPTASE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 51-45-6 (HISTAMINE)
97501-93-4 (TRYPTASE)

L65 ANSWER 18 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:96884 BIOSIS
DN PREV199598111184
TI The effects of SCF on melanocyte differentiation in neural crest culture.

AU Kawa, Yoko (1); Ono, Hirotake; Sato, Mitsuhiro (1); Kubota, Yasuo (1); Takeuchi, Takuji; Mizoguchi, Masako (1)
CS (1) Dep. Dermatol., St. Marianna Univ. Sch. Med., Kawasaki 216 Japan
SO Pigment Cell Research, (1994) Vol. 7, No. 5, pp. 368.
Meeting Info.: 9th Annual Meeting of the Japanese Society for Pigment Cell Research Tokyo, Japan December 9-10, 1994
ISSN: 0893-5785.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Reproductive System - Physiology and Biochemistry 16504
Endocrine System - General *17002
Integumentary System - Physiology and Biochemistry *18504
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Morphogenesis, General *25508
In Vitro Studies, Cellular and Subcellular *32600
BC Muridae *86375
IT Major Concepts
Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis)
IT Miscellaneous Descriptors
C-KIT; DERMIS; EMBRYOGENESIS; MEETING ABSTRACT; **PIGMENT** CELL; **STEM CELL FACTOR**
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

L65 ANSWER 19 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:96876 BIOSIS
DN PREV199598111176
TI Cloning and sequence analysis of the cDNA encoding **C-kit** gene of the Shiba goat (Capra hircus) with dominant black-eyed white phenotype.
AU Tanaka, Satoshi (1); Tojo, Hideaki (1); Kim, Yong-Jin (1); Tujimura, Tohru; Kitamura, Yukihiko; Tachi, Chikashi (1)
CS (1) Dep. Applied Genet., Inst. Anim. Resour. Sci., Grad. Sch. Agric. Life Sci., Univ. Tokyo, Bunkyo-ku, Tokyo 113 Japan
SO Pigment Cell Research, (1994) Vol. 7, No. 5, pp. 366.
Meeting Info.: 9th Annual Meeting of the Japanese Society for Pigment Cell Research Tokyo, Japan December 9-10, 1994
ISSN: 0893-5785.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Endocrine System - General *17002
Integumentary System - Physiology and Biochemistry *18504
Sense Organs, Associated Structures and Functions - Physiology and Biochemistry *20004
BC Bovidae *85715
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Genetics; Integumentary System (Chemical Coordination and Homeostasis); Sense Organs (Sensory Reception)

IT Chemicals & Biochemicals
ALANINE
IT Miscellaneous Descriptors
ALANINE INSERTION; COMPLEMENTARY DNA; MEETING ABSTRACT; MELANOCYTE; **PIGMENT** CELL
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Bovidae (Bovidae)
ORGN Organism Superterms
animals; artiodactyls; chordates; mammals; nonhuman vertebrates; nonhuman mammals; vertebrates
RN 56-41-7 (ALANINE)

L65 ANSWER 20 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:150493 BIOSIS
DN PREV199497163493
TI Recombinant human **stem cell factor** (rhSCF) induces cutaneous mast cell activation and hyperplasia, and **hyperpigmentation** in humans in vivo.
AU Costa, J. J.; Demetri, G. D.; Harrist, T. J.; Dvorak, A. M.; Hayes, D. F.; Merica, E. A.; Menchaca, D. M.; Gringeri, A. J.; Galli, S. J.
CS Boston, MA USA
SO Journal of Allergy and Clinical Immunology, (1994) Vol. 93, No. 1 PART 2, pp. 225.
Meeting Info.: Fiftieth Annual Meeting of the American Academy of Allergy and Immunology Anaheim, California, USA March 4-9, 1994
ISSN: 0091-6749.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Endocrine System - General *17002
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Allergy *35500
BC Diptera 75314
Hominidae *86215
IT Major Concepts
Allergy (Clinical Immunology, Human Medicine, Medical Sciences); Biochemistry and Molecular Biophysics; Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
ALLERGY; MEETING ABSTRACT
ORGN Super Taxa
Diptera: Insecta, Arthropoda, Invertebrata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Diptera (Diptera)
ORGN Organism Superterms
animals; arthropods; chordates; humans; insects; invertebrates; mammals; primates; vertebrates

L65 ANSWER 21 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:49831 BIOSIS
DN PREV199497062831
TI The expression of oncogene **c-kit** and ret in **pigment** cells.

AU Ohashi, Akiko; Funasaka, Yoko; Ueda, Masato; Ichihashi, Masamitsu
CS Dep. Dermatol., Kobe Univ. Japan
SO Pigment Cell Research, (1993) Vol. 6, No. 5, pp. 376.
Meeting Info.: 8th Annual Meeting of the Japanese Society for Pigment Cell Research Aichi, Japan December 10-11, 1993
ISSN: 0893-5785.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Replication, Transcription, Translation *10300
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Integumentary System - Pathology *18506
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Biochemistry *24006
BC Vertebrata - Unspecified *85150
IT Major Concepts
Cell Biology; Genetics; Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Molecular Genetics (Biochemistry and Molecular Biophysics); Tumor Biology
IT Miscellaneous Descriptors
MEETING ABSTRACT; MELANOCYTE; NEVUS CELL; TUMOR PROGRESSION
ORGN Super Taxa
Vertebrata - Unspecified: Vertebrata, Chordata, Animalia
ORGN Organism Name
Vertebrata (Vertebrata - Unspecified)
ORGN Organism Superterms
animals; chordates; nonhuman vertebrates; vertebrates

L65 ANSWER 22 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:538275 BIOSIS
DN PREV199345125369
TI Expression of tyrosinase, tyrosinase-related protein 1 and 2, **C-kit** and **C-kit** ligand in vitro and in vivo.
AU Sakai, Chie; Kameyama, Koichiro
CS Dep. Dermatol., Kitasato Inst. Med. Cent. Hosp., Saitama Japan
SO Journal of Investigative Dermatology, (1993) Vol. 101, No. 3, pp. 394.
Meeting Info.: Second Tricontinental Meeting of the JSID (Japanese Society for Investigative Dermatology), SID (Society for Investigative Dermatology, Inc.), and ESDR (European Society for Dermatological Research) Kyoto, Japan October 28-31, 1993
ISSN: 0022-202X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Integumentary System - Pathology *18506
In Vitro Studies, Cellular and Subcellular *32600
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Dermatology (Human Medicine, Medical Sciences); Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
TYROSINASE
IT Miscellaneous Descriptors
ABSTRACT; **HYPERPIGMENTED** DISORDER; MELANOBLAST

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 9002-10-2 (TYROSINASE)

L65 ANSWER 23 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:179863 BIOSIS
DN PREV199344087463
TI Expression of IL-4 mRNA in human dermal mast cells in response to Fc receptor crosslinkage in the presence of SCF.
AU Okayama, Y. (1); Quint, D.; Hunt, T. C. (1); El-Lati, S. (1); Heusser, C. H.; Bullock, G.; Mueller, R.; Bradding, P. (1); Howarth, P. (1); et al.
CS (1) Immunopharmacol. Group, University Southampton UK
SO Journal of Allergy and Clinical Immunology, (1993) Vol. 91, No. 1 PART 2, pp. 256.
Meeting Info.: Forty-ninth Annual Meeting of the American Academy of Allergy and Immunology Chicago, Illinois, USA March 12-17, 1993
ISSN: 0091-6749.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Replication, Transcription, Translation *10300
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Endocrine System - General *17002
Integumentary System - Pathology *18506
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Allergy *35500
BC Hominidae *86215
IT Major Concepts
Allergy (Clinical Immunology, Human Medicine, Medical Sciences); Blood and Lymphatics (Transport and Circulation); Clinical Immunology (Human Medicine, Medical Sciences); Dermatology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Genetics; Molecular Genetics (Biochemistry and Molecular Biophysics); Pathology
IT Miscellaneous Descriptors
ABSTRACT; ALLERGY; **INFLAMMATION**; INTERLEUKIN-4 MESSENGER RNA; PATHOGENESIS; **STEM CELL FACTOR**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L65 ANSWER 24 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:113013 BIOSIS
DN PREV199344055413
TI Proliferation and neoplastic transformation of **pigment** cells in metallothionein/ret transgenic mice.
AU Takahashi, Masahide (1); Iwamoto, Takashi; Nakashima, Izumi
CS (1) Dep. Pathol., Nagoya Univ. Sch. Med., 65 Tsurumai-cho, Showa-ku, Nagoya 466 Japan
SO Pigment Cell Research, (1992) Vol. 5, No. 5 PART 2, pp. 344-347.

Meeting Info.: Symposium on Molecular Biology of Pigment Cells Sendai, Japan November 8-9, 1990
ISSN: 0893-5785.
DT Article
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Integumentary System - Pathology *18506
Neoplasms and Neoplastic Agents - Carcinogens and Carcinogenesis *24007
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Morphogenesis, General *25508
BC Muridae *86375
IT Major Concepts
Cell Biology; Development; Genetics; Integumentary System (Chemical Coordination and Homeostasis); Tumor Biology
IT Miscellaneous Descriptors
C-KIT PROTO-ONCOGENE;
DEVELOPMENT; MELANOCYTIC TUMOR; MELANOGENESIS; ONCOGENE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates

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L66 ANSWER 1 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:456953 BIOSIS
DN PREV199900456953
TI Zebrafish sparse corresponds to an orthologue of **c-kit** and is required for the morphogenesis of a subpopulation of melanocytes, but is not essential for hematopoiesis or primordial germ cell development.
AU Parichy, David M. (1); Rawls, John F.; Pratt, Stephen J.; Whitfield, Tanya T.; Johnson, Stephen L.
CS (1) Department of Genetics, Washington University School of Medicine, 4566 Scott Avenue, Saint Louis, MO, 63110 USA
SO Development (Cambridge), (**Aug., 1999**) Vol. 126, No. 15, pp. 3425-3436.
ISSN: 0950-1991.
DT Article
LA English
SL English
AB The relative roles of the Kit receptor in promoting the migration and survival of amniote melanocytes are unresolved. We show that, in the zebrafish, Danio rerio, the **pigment** pattern mutation sparse corresponds to an orthologue of **c-kit**. This finding allows us to further elucidate morphogenetic roles for this **c-kit**-related gene in melanocyte morphogenesis. Our analyses of zebrafish melanocyte development demonstrate that the **c-kit** orthologue identified in this study is required both for normal migration and for survival of embryonic melanocytes. We also find that, in contrast to mouse, the zebrafish **c-kit** gene that we have identified is not essential for hematopoiesis or primordial germ cell development. These unexpected differences may reflect evolutionary divergence in **c-kit** functions following gene duplication events in teleosts.

L66 ANSWER 2 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:420883 BIOSIS

DN PREV199900420883
TI Lack of **c-kit** mutation in familial urticaria **pigmentosa**.
AU Rosbotham, J. L. (1); Malik, N. M.; Syrris, P.; Jeffery, S.; Bedlow, A.; Gharraie, S.; Murday, V. A.; Holden, C. A.; Carter, N. D.
CS (1) Department of Dermatology, St George's Hospital, London, SW17 0QT UK
SO British Journal of Dermatology, (**May, 1999**) Vol. 140, No. 5, pp. 849-852.
ISSN: 0007-0963.
DT Article
LA English
SL English
AB Somatic mutations within **c-kit** have been reported in individuals with mastocytoses, including urticaria **pigmentosa** (UP). We have identified three siblings with UP. We aimed to determine whether the **c-kit proto-oncogene** was playing a part in the aetiology of UP in these three siblings. Using seven microsatellite repeat markers spanning an 8-cM interval encompassing the **c-kit** gene we followed the transmission of the **c-kit** gene in this family. Furthermore, single-strand conformation polymorphism analysis was used to scan exon 17 of the **c-kit** gene for mutations in genomic DNA of all family members and somatic DNA extracted from skin of the eldest affected sibling, the proband. No mutations were found in exon 17 in either genomic DNA of all family members or somatic DNA of the proband. Patients with UP have been shown to possess somatic mutations of the **c-kit** gene. However, this locus has been excluded as playing a part in the three siblings examined here in whom a second gene locus must bedetermining their UP. Therefore, this study emphasizes genetic heterogeneity in UP. Future study to identify primary molecular determinants of UP should include affected sib-pair studies.

L66 ANSWER 3 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:346845 BIOSIS
DN PREV199900346845
TI Analysis of **c-kit** exon 11 and exon 17 of urticaria **pigmentosa** that occurred in monozygotic with twin sisters.
AU Sato-Matsumura, K. C. (1); Matsumura, T. (1); Koizumi, H. (1); Sato, H.; Nagashima, K.; Ohkawara, A. (1)
CS (1) Department of Dermatology, Hokkaido University School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo, 060-8638 Japan
SO British Journal of Dermatology, (**June, 1999**) Vol. 140, No. 6, pp. 1130-1132.
ISSN: 0007-0963.
DT Article
LA English
SL English
AB Genomic DNA extracted from peripheral blood mononuclear cells of monozygotic twin patients with urticaria **pigmentosa** was investigated for mutations of **proto-oncogene c-kit**. Neither the patients nor their families had genomic mutations in exon 11 or exon 17 of **c-kit**. The patients did not have any systemic involvement or bone marrow abnormalities. There are indications that some genetic factors may participate in the pathogenesis of urticaria **pigmentosa** in monozygotic twins. In the present patients, factors other than genomic faults in exon 11 and exon 17 of **c-kit** may be responsible for the pathogenesis.

L66 ANSWER 4 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:330866 BIOSIS
DN PREV199900330866
TI Increased serum level of **stem cell factor** in association with disease progression of **hyperpigmented** mycosis fungoides.
AU Yamamoto, T. (1); Katayama, I.; Nishioka, K. (1)

CS (1) Tokyo Medical and Dental University, School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113 Japan
SO British Journal of Dermatology, (**April, 1999**) Vol. 140, No. 4, pp. 765-766.
ISSN: 0007-0963.
DT Article; Letter
LA English

L66 ANSWER 5 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:326565 BIOSIS
DN PREV199900326565
TI Genetic analysis of steel and the PG-M/versican-encoding gene AxPG as candidates for the white (d) **pigmentation** mutant in the salamander Ambystoma mexicanum.
AU Parichy, David M. (1); Stigson, Michael; Voss, S. Randal
CS (1) Department of Genetics, Washington University School of Medicine, 4566 Scott Avenue, Saint Louis, MO, 63110 USA
SO Development Genes and Evolution, (**June, 1999**) Vol. 209, No. 6, pp. 349-356.
ISSN: 0949-944X.
DT Article
LA English
SL English
AB Vertebrate non-retinal **pigment** cells are derived from neural crest (NC) cells, and several mutations have been identified in the Mexican axolotl Ambystoma mexicanum (Ambystomatidae) that affect the development of these cell lineages. In "white" (d) mutant axolotls, premigratory NC cells differentiate as **pigment** cells, yet fail to disperse, survive, or both, and this leads to a nearly complete absence of **pigment** cells in the skin. Previous studies revealed that d affects **pigment** cell development non-autonomously, and have reported differences between white and wild-type axolotls in the structure and composition of the extracellular matrix through which NC and **pigment** cells migrate. Here we test the correspondence of d and two candidate genes: steel and AxPG. In amniotes, Steel encodes the cytokine Steel factor (mast cell growth factor; **stem cell factor**; kit ligand), which is expressed along the migratory pathways of melanocyte precursors and is required by these cells for their migration and survival; mammalian Steel mutants resemble white mutant axolotls in having a deficit or complete absence of **pigment** cells. In contrast, AxPG encodes a PG-M/versican-like proteoglycan that may promote the migration of A. mexicanum **pigment** cells, and AxPG expression is reduced in white mutant axolotls. We cloned a salamander orthologue of steel and used a partial genetic linkage map of Ambystoma to determine the genomic locations of steel, AxPG, and d. We show that the three genes map to different linkage groups, excluding steel and AxPG as candidates for d.

L66 ANSWER 6 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:326510 BIOSIS
DN PREV199900326510
TI Altered cell-surface targeting of **stem cell factor** causes loss of melanocyte precursors in Steel17H mutant mice.
AU Wehrle-Haller, Bernhard (1); Weston, James A.
CS (1) Department of Pathology, Centre Medical Universitaire, 1, Rue Michel-Servet, 1211, Geneva 4 Switzerland
SO Developmental Biology, (**June 1, 1999**) Vol. 210, No. 1, pp. 71-86.
ISSN: 0012-1606.
DT Article
LA English
SL English
AB The normal products of the murine Steel (Sl) and Dominant white spotting (W) genes are essential for the development of melanocyte precursors, germ cells, and hematopoietic cells. The Sl locus encodes **stem**

cell factor (SCF), which is the ligand of **c-kit**, a receptor tyrosine kinase encoded by the W locus. One allele of the S1 mutation, S117H, exhibits minor hematopoietic defects, sterility only in males, and a complete absence of coat **pigmentation**. The S117H gene encodes SCF protein which exhibits an altered cytoplasmic domain due to a splicing defect. In this paper we analyzed the mechanism by which the **pigmentation** phenotype in S117H mutant mice occurs. We show that in embryos homozygous for S117H the number of melanocyte precursors is severely reduced on the lateral neural crest migration pathway by e11.5 and can no longer be detected by e13.5 when they would enter the epidermis in wildtype embryos. The reduced number of dispersing melanocyte precursors correlates with areduction of SCF immunoreactivity in mutant embryos in all tissues examined. Regardless of the reduced amount, functional SCF is present at the cell surface of fibroblasts transfected with S117H mutant SCF cDNA. Since SCF immunoreactivity normally accumulates in basolateral compartments of SCF-expressing embryonic epithelial tissues, we analyzed the localization of wildtype and S117H mutant SCF protein in transfected epithelial (MDCK) cells in vitro. As expected, wildtype forms of SCF localize to and are secreted from the basolateral compartment. In contrast, mutant forms of SCF, which either lack a membrane anchor or exhibit the S117H altered cytoplasmic tail, localize to and are secreted from the apical compartment of the cultured epithelium. We suggest, therefore, that the loss of melanocyte precursors prior to epidermal invasion, and the loss of germ cells from mature testis, can be explained by the inability of S117H mutant SCF to be targeted to the basolateral compartment of polarized epithelial keratinocytes and Sertoli cells, respectively.

L66 ANSWER 7 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:303139 BIOSIS
DN PREV199900303139
TI Comparison of genetic and immunohistochemical findings in childhood and adult onset urticaria **pigmentosa**.
AU Buettner, Claudia (1); Grabbe, Juergen; Haas, Norbert; Sepp, Norbert T.; Kunkel, Gert; Henz, Beate M.
CS (1) Campus Virchow-Klinikum, Charite, Asthmapoliklinik, Augustenburger Platz 1, D-13353, Berlin Germany
SO International Archives of Allergy and Immunology, (**Feb.-April, 1999**) Vol. 118, No. 2-4, pp. 206-207.
ISSN: 1018-2438.
DT Article
LA English

L66 ANSWER 8 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:264678 BIOSIS
DN PREV199900264678
TI Removal of **stem cell factor** or addition of monoclonal anti-**c-KIT** antibody induces apoptosis in murine **melanocyte** precursors.
AU Ito, Masaru (1); Kawa, Yoko; Ono, Hirotake; Okura, Mitsuhiro; Baba, Takako; Kubota, Yasuo; Nishikawa, Sin-Ichi; Mizoguchi, Masako
CS (1) Department of Dermatology, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyarnae-ku, Kawasaki, 216-8511 Japan
SO Journal of Investigative Dermatology, (**May, 1999**) Vol. 112, No. 5, pp. 796-801.
ISSN: 0022-202X.
DT Article
LA English
SL English
AB Previous findings indicate that the protein **c-KIT** and its ligand, **stem cell factor** (SCF) play a crucial role in the development of **melanocytes** from their precursors in the embryonic neural crest cells. Using a monoclonal anti-**c-KIT** antibody, ACK2, which is an antagonistic blocker of **c-KIT** function, we and others demonstrated that mouse **melanocytes** disappeared with the injection of ACK2 during

certain periods of embryonic and postnatal life. The precise mechanisms of this disappearance, however, remain unclear. Because **melanocytes** disappeared without any **inflammation** in these in vivo studies, we suspect that apoptosis was a main cause of their disappearance. In this study, to clarify the underlying mechanism, we studied whether ACK2 induces apoptosis in **c-KIT**-positive melanoblasts, which appear in mouse neural crest cells cultured with SCF from 9.5 d old mouse embryos. With an in situ apoptosis detection kit, a significant increase in apoptosis was detected after the removal of SCF, which further increased with the addition of ACK2 during SCF-dependent periods. The occurrence of apoptosis in the cultured cells was also demonstrated by a DNA analysis and electron microscopy. Immunohistochemical double staining confirmed that the apoptotic cells were **c-KIT** positive, and the electron microscopy showed that these apoptotic cells were **melanocyte** precursors. It was therefore demonstrated that apoptosis was induced in the SCF-dependent **c-KIT** -positive **melanocytes** in vitro when the SCF/**c-KIT** interaction was obstructed. These findings elucidate the mechanism of the regulation of **melanocyte** development, and the survival and proliferation of these precursor cells, by SCF/**c-KIT** interaction.

L66 ANSWER 9 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:249324 BIOSIS
DN PREV199900249324
TI Increased cutaneous immunoreactive **stem cell factor** expression and serum **stem cell factor** level in systemic scleroderma.
AU Kihira, Chika; Mizutani, Hitoshi (1); Asahi, Kunihiko; Hamanaka, Hiroko; Shimizu, Masayuki
CS (1) Department of Dermatology, Faculty of Medicine, Mie University, Tsu, Mie, 5148507 Japan
SO Journal of Dermatological Science, (**May, 1999**) Vol. 20, No. 1, pp. 72-78.
ISSN: 0923-1811.
DT Article
LA English
SL English
AB Skin **hyperpigmentation** and itching are characteristic findings in systemic sclerosis (SSC) patients. **Stem cell factor** (SCF, **c-kit** ligand) is a multifunctional cytokine which can promote melanocyte and mast cell development. We investigated the SCF expression histopathologically in normal and SSC skin, and compared the expression with the serum SCF levels measured with a specific enzyme-linked immunosorbent assay. The epidermal and dermal immunoreactive SCF expression was markedly higher in the forearm skin of edematous phase SSC patients than in that of normal subjects. Tissue SCF expression declined from the sclerotic phase to the atrophic phase, where it was close to the normal level. In contrast, the elevated serum SCF level seen in the edematous phase samples was further increased in the sclerotic phase samples. The serum SCF level decreased in the atrophic phase, but it still remained at a level higher than that of the normal controls. Itching and increase of dermal mast cell number are characteristic of edematous phase SSC, and are in bears a parallel to the presently observed dermal SCF expression profile. **Pigmentation** is significant in sclerotic phase SSC and lasts to the atrophic phase, which may correspond to the serum SCF level observed here. These results indicate a contribution of the fibroblast membrane integral SCF in dermal mast cell development, and of the soluble serum SCF to melanocyte activation in SSC.

L66 ANSWER 10 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:49183 BIOSIS
DN PREV199900049183
TI Development of melanocyte progenitors in murine steel mutant neural crest explants cultured with **stem cell factor**,

endothelin-3, or TPA.
AU Ono, Hirotake (1); Kawa, Yoko; Asano, Mari; Ito, Masaru; Takano, Atsuko; Kubota, Yasuo; Matsumoto, Jiro; Mizoguchi, Masako
CS (1) Dep. Biol., Keio Univ., 4-1-1 Hiyoshi, Kohoku-ku, Yokohama 223-8521 Japan
SO Pigment Cell Research, (**Oct., 1998**) Vol. 11, No. 5, pp. 291-298. ISSN: 0893-5785.
DT Article
LA English
AB **Stem cell factor** (SCF) has been suggested to be indispensable for the development of neural crest cells into melanocytes because Steel mutant mice (i.e., Sl/Sld) have no **pigmented** hairs. On the other hand, it has been demonstrated that the addition of endothelin 3 (ET-3) or TPA to neural crest cell cultures can induce melanocyte differentiation without addition of extrinsic SCF In this study, we excluded the influence of intrinsic SCF by using Sl/Sl mouse embryos to study more precisely the effects of natural cytokines, such as extrinsic soluble SCF or ET-3, or chemical reagents, such as TPA or cholera toxin. We found that SCF is supplied within the wild-type neural crest explants and that ET-3 cannot induce melanocyte differentiation or proliferation without SCF. These results indicate that SCF plays a critical role in survival or G1/S entry of melanocyte progenitors and that SCF initially stimulates their proliferation and then ET-3 accelerates their proliferation and differentiation. TPA has the ability to elicit neural crest cell differentiation into melanocytes without exogenously added SCF but it is not as effective as SCF because many more melanocytes developed in the wild-type neural crest explants cultured with TPA.

L66 ANSWER 11 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:37290 BIOSIS
DN PREV199900037290
TI Targeting the microphthalmia basic helix-loop-helix-leucine zipper transcription factor to a subset of E-box elements in vitro and in vivo.
AU Aksan, I.; Goding, C. R. (1)
CS (1) Eukaryotic Transcription Lab., Marie Curie Res. Inst., The Chart, Oxted, Surrey RH8 0TL UK
SO Molecular and Cellular Biology, (**Dec., 1998**) Vol. 18, No. 12, pp. 6930-6938. ISSN: 0270-7306.
DT Article
LA English
AB The development of melanocytes, which are **pigment**-producing cells responsible for skin, hair, and eye color, is absolutely dependent on the action of the microphthalmia basic helix-loop-helix-leucine zipper (bHLH-LZ) transcription factor (Mi); mice lacking a functional Mi protein are entirely devoid of **pigment** cells. Mi has been shown to activate transcription of the tyrosinase, TRP-1, TRP-2, and QNR-71 genes through specific E-box elements, most notably the highly conserved M box. We investigated the mechanism which enables Mi to be recruited specifically to a restricted subset of E boxes in target promoters while being prevented from binding E-box elements in other promoters. We show both in vitro and in vivo that the presence of a T residue flanking a CATGTG E box is an essential determinant of the ability of Mi to bind DNA, and we successfully predict that the CATGTG E box from the P gene would not bind Mi. In contrast, no specific requirement for the sequences flanking a CACGTG E box was observed, and no binding to an atypical E box in the **c-Kit** promoter was detected. The relevance of these observations to the control of melanocyte-specific gene expression was highlighted by the fact that the E-box elements located in the tyrosinase, TRP-1, TRP-2, and QNR-71 promoters without exception possess a 5' flanking T residue which is entirely conserved between species as diverse as man and turtle. The ability of Mi to discriminate between different E-box motifs provides a mechanism to restrict the repertoire of genes which are likely to be regulated by Mi and provides insight into the ability of bHLH-LZ transcription factors to achieve the specificity

required for the precise coordination of transcription during development.

L66 ANSWER 12 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:434522 BIOSIS
DN PREV199800434522
TI Transgene expression of steel factor in the basal layer of epidermis promotes survival, proliferation, differentiation and migration of melanocyte precursors.
AU Kunisada, Takahiro (1); Yoshida, Hisahiro; Yamazaki, Hidetoshi; Miyamoto, Akitomo; Hemmi, Hiroaki; Nishimura, Emi; Shultz, Leonard D.; Nishikawa, Shin-Ichi; Hayashi, Shin-Ichi
CS (1) Dep. Immunol., Sch. Life Sci., Fac. Med., Tottori Univ., Nishi-machi 86, Yonago 683 Japan
SO Development (Cambridge), (**Aug., 1998**) Vol. 125, No. 15, pp. 2915-2923.
ISSN: 0950-1991.
DT Article
LA English
AB Mutations at the murine dominant white spotting (KitW) and steel (MgfSl) loci, encoding **c-Kit** receptor kinase and its ligand respectively, exert developmental defects on hematopoietic cells, melanocytes, germ cells and interstitial cells of Cajal. The expression patterns of steel factor (SLF) observed in the skin and gonads suggest that SLF mediates a migratory or a chemotactic signal for **c-Kit**-expressing stem cells (melanocyte precursors and primordial germ cells). By targeting expression of SLF to epidermal keratinocytes in mice, we observed extended distribution of melanocytes in a number of sites including oral epithelium and footpads where neither melanocytes nor their precursors are normally detected. In addition, enlarged **pigmented** spots of KitW and other spotting mutant mice were observed in the presence of the SLF transgene. These results provide direct evidence that SLF stimulates migration of melanocytes in vivo. We also present data suggesting that SLF does not simply support survival and proliferation of melanocytes but also promotes differentiation of these cells. Unexpectedly, melanocyte stem cells independent of the **c-Kit** signal were maintained in the skin of the SLF transgenic mice. After the elimination of **c-Kit**-dependent melanoblasts by function-blocking anti-**c-Kit** antibody, these stem cells continued to proliferate and differentiate into mature melanocytes. These melanoblasts are able to migrate to cover most of the epidermis after several months. The SLF transgenic mice described in this report will be useful in the study of melanocyte biology.

L66 ANSWER 13 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:362810 BIOSIS
DN PREV199800362810
TI Ultrastructural analysis of human skin biopsy specimens from patients receiving recombinant human **stem cell factor** : Subcutaneous injection of rhSCF induces dermal mast cell degranulation and granulocyte recruitment at the injection site.
AU Dvorak, Ann M. (1); Costa, John J.; Monahan-Earley, Rita A.; Fox, Patricia; Galli, Stephen J.
CS (1) Dep. Pathol./East Campus, Beth Israel Deaconess Med. Cent., 330 Brookline Ave., Boston, MA 02215 USA
SO Journal of Allergy and Clinical Immunology, (**June, 1998**) Vol. 101, No. 6 PART 1, pp. 793-806.
ISSN: 0091-6749.
DT Article
LA English
AB We performed an ultrastructural analysis of 10 skin biopsy specimens that had been obtained from three women who were undergoing daily subcutaneous dosing with recombinant methionyl-human **stem cell factor** (rhSCF) as part of a phase I clinical trial. The biopsy specimens were obtained at sites of subcutaneous administration of rhSCF, within approximately 1 to 2 hours of rhSCF injection, and, at the same time, at contralateral control sites that had not been directly injected

with rhSCF. We previously reported that subcutaneous dosing with rhSCF in these subjects induced the local development of a wheal and flare response, which was associated with evidence of mast cell degranulation, as well as a systemic increase in numbers of cutaneous mast cells. The present election microscopic analysis revealed that all biopsies of swollen, erythematous rhSCF-injected sites exhibited anaphylactic degranulation of both mature and immature mast cells, an acute **inflammatory** response characterized by the migration of neutrophils, basophils (some of which exhibited evidence of piecemeal degranulation), and eosinophils through blood vessel walls into the perivascular and extravascular spaces, and edema and fibrin deposition within the interstitium. By contrast, the control biopsies contained no evidence of mast cell degranulation or acute **inflammation**. However, both control and rhSCF-injected sites exhibited mast cells that were undergoing granule building and maturation. Thus at the doses tested in these subjects, subcutaneous injection of rhSCF induced anaphylactic-type degranulation of dermal mast cells at the injection site, with an acute **inflammatory** response that was associated with the recruitment of granulocytes. By contrast, mast cells at sites distant from those directly injected with rhSCF exhibited no evidence of enhanced secretion.

L66 ANSWER 14 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:212701 BIOSIS
DN PREV199800212701
TI Biological characterization of human fibroblast-derived mitogenic factors for human **melanocytes**.
AU Imokawa, Genji (1); Yada, Yukihiro; Morisaki, Naoko; Kimura, Mitsutoshi
CS (1) Biol. Sci. Lab., Kao Corp., Ichikaimachi 2606, Haga, Tochigi 321-34 Japan
SO Biochemical Journal, (**March 15, 1998**) Vol. 330, No. 3, pp. 1235-1239.
ISSN: 0264-6021.
DT Article
LA English
AB To clarify the paracrine linkage between human fibroblasts and **melanocytes** in cutaneous **pigmentation**, we studied the effects of human fibroblast-derived factors on the proliferation of human **melanocytes**. In medium conditioned for 4 days with human fibroblast culture, factors were produced that markedly stimulated DNA synthesis of human **melanocytes**. The stimulatory effect was higher in medium conditioned with fibroblasts from aged skin than in medium conditioned with fibroblasts from young skin, and was interrupted by inhibitors of tyrosine kinase, such as tyrphostin, genistein and herbimycin, but not by inhibitors of protein kinases C and A, such as H-7 and phloretin. The conditioned medium was also capable of activating mitogen-activated protein kinase of human **melanocytes**, with old fibroblasts being more effective than young ones. Analysis of factors released into the conditioned medium revealed that levels of hepatocyte growth factor (HGF) and **stem cell factor** (SCF) were increased in old-fibroblast-conditioned medium compared with young-fibroblast-conditioned medium. In contrast, levels of basic fibroblast growth factor (bFGF) were similar in both media. When the conditioned medium was treated with HGF antibody with or without SCF antibody, the increase in DNA synthesis by human **melanocytes** was decreased to 20% of the elevated level, whereas antibodies to bFGF had no effect. Analysis of the medium conditioned for 4 days after cytokine application demonstrated that, of the cytokines tested, interleukin 1a and tumour necrosis factor a are highly effective in stimulating HGF secretion by old fibroblasts. HGF and SCF, but not bFGF, were markedly increased in culture medium in the presence of IL-1alpha, and this stimulatory effect was confined to young human fibroblasts. These findings suggest that SCF and HGF derived from human fibroblasts may play a part in regulating cutaneous **pigmentation** during **inflammation** and aging.

L66 ANSWER 15 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:94372 BIOSIS
DN PREV199800094372
TI MAP kinase links the transcription factor Microphthalmia to **c-Kit** signalling in melanocytes.
AU Hemesath, Timothy J.; Price, E. Roydon; Takemoto, Clifford; Badalian, Tina; Fisher, David E. (1)
CS (1) Dana Farber Cancer Inst., Harvard Med. Sch., 44 Binney St., Boston, MA 02115 USA
SO Nature (London), (**Jan. 15, 1998**) Vol. 391, No. 6664, pp. 298-301.
ISSN: 0028-0836.
DT Article
LA English
AB Germline mutations at loci encoding the transcription factor Microphthalmia (Mi), the cytokine receptor **c-Kit**, or its ligand Steel factor (SI) result in strikingly similar defects in mast cell and melanocyte development. Here we describe a biochemical link between Kit signalling and the activity of Mi. Stimulation of melanoma cells with Sl results in activation of MAP kinase, which in turn phosphorylates NU at a consensus target serine. This phosphorylation upregulates Mi transactivation of the tyrosinase **pigmentation** gene promoter. In addition to modulating **pigment** production, such signalling may regulate the expression of genes essential for melanocyte survival and development. The pathway represents a new application of the general MAP kinase machinery in transducing a signal between a tissue-specific receptor at the cell surface and a tissue-specific transcription factor in the nucleus.

L66 ANSWER 16 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:94282 BIOSIS
DN PREV199800094282
TI Why do the mastocytoses in children heal and why do they not in adults.
AU Guillaume, J.-C (1)
CS (1) Clin. Dermatol., Hop. Pasteur, 39 avenue de la Liberte, F-68024 Colmar Cedex France
SO Annales de Dermatologie et de Venereologie, (**Nov., 1997**) Vol. 124, No. 11, pp. 787-788.
ISSN: 0151-9638.
DT Article
LA French

L66 ANSWER 17 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:515842 BIOSIS
DN PREV199799815045
TI The predominant defect in dilute melanocytes is in melanosome distribution and not cell shape, supporting a role for myosin V in melanosome transport.
AU Wei, Qin; Wu, Xufeng; Hammer, John A., III (1)
CS (1) Lab. Cell Biology, Section Molecular Cell Biology, National Heart Lung and Blood Inst., National Inst. Health, Bethesda, MD 20892-0301 USA
SO Journal of Muscle Research and Cell Motility, (1997) Vol. 18, No. 5, pp. 517-527.
ISSN: 0142-4319.
DT Article
LA English
AB Mice with mutations at the dilute locus, which encodes the heavy chain of a type V unconventional myosin, exhibit a reduction in coat colour intensity. This defect is thought to be caused by the absence in dilute melanocytes of the extensive dendritic arbor through which these cells normally deliver **pigment**-laden melanosomes to keratinocytes. The data on which this conclusion has been based can also be explained, however, by a defect in the outward transport of melanosomes within melanocytes of normal shape. To resolve this question, we compared the shape and **pigment** distribution within melanocytes present in primary cultures prepared from the epidermis of C57BL/6J pups that were either wild type (D/D) at dilute or homozygous for the dilute null allele

d-120J. These same comparisons were also performed on melanocytes in situ, where antibodies to the membrane tyrosine kinase receptor **cKIT** were used to visualize melanocyte cell shape independent of **pigment** distribution. Wild type melanocytes were found to be dendritic and to have melanosomes distributed throughout their dendrites both in vitro and in situ. Mutant melanocytes were also found to be dendritic in both cases, but their melanosomes were highly concentrated in the cell body and largely excluded from dendrites. We conclude, therefore, that the predominant defect in dilute melanocytes is in melanosome distribution, not cell shape. These results argue that the myosin V isoform encoded by the dilute locus functions in dendritic extensions to move melanosomes from their site of formation within the cell body to their site of intercellular transfer at dendritic tips. This conclusion is consistent with our recent demonstration by immunolocalization that the dilute myosin V isoform associates with melanosomes in mouse melanocytes.

L66 ANSWER 18 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:496856 BIOSIS
DN PREV199799796059
TI Overexpression of human **stem cell factor** impairs melanocyte, mast cell, and thymocyte development: A role for receptor tyrosine kinase-mediated mitogen activated protein kinase activation in cell differentiation.
AU Kapur, Reuben; Everett, Eric T.; Uffman, Josh; McAndrews-Hil, Monica; Cooper, Ryan; Ryder, John; Vik, Terry; Williams, David A. (1)
CS (1) Herman B. Wells Cent. Pediatric Res., Howard Hughes Med. Inst., Cancer Res. Build., 1044 W. Walnut, Room 402C, Indianapolis, IN 46202-5225 USA
SO Blood, (1997) Vol. 90, No. 8, pp. 3018-3026.
ISSN: 0006-4971.
DT Article
LA English
AB **Stem cell factor** (SCF) is synthesized as both soluble (S) and membrane-associated (MA) proteins. Indirect insight into the function of MA and S isoforms of SCF has come from studies performed in Steel (SI) mutant mice. However, the physiologic role(s) of these two isoforms remain unknown. In an attempt to better understand the in vivo role of **c-kit**/SCF interactions on various cell lineages, transgenic mice were generated that overexpress MA isoform of human SCF (hSCF). In murine cells, hSCF behaves as an antagonist to normal SCF function, due to interference with the interaction between endogenous murine SCF and its receptor, **c-kit**, encoded by the dominant white spotting (W) gene. Mice expressing the hSCF transgene display a variety of phenotypic abnormalities, which are accentuated when combined with W alleles. Here we show that mice homozygous for the hSCF transgene demonstrate a coat color deficiency seen in some mice homozygous for mild W alleles. Specifically, homozygous hSCF transgenic mice (hSCF-220) display a pronounced forehead blaze, with additional white spots over the cervical region, as well as a very large belly spot. Doubly heterozygous animals that carry both a mutated W allele and the hSCF transgene also display an unusual **pigment** defect and a dramatic reduction in the number of dermal mast cells. Furthermore, overexpression of MA hSCF in the thymus results in abnormal thymocyte differentiation and proliferation, which is associated with reduced mitogen activated protein (MAP) kinase activation. Thus, MAP kinase activation by a receptor tyrosine kinase, such as **c-kit**, may be critical for the differentiation of thymocytes in vivo.

L66 ANSWER 19 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:415860 BIOSIS
DN PREV199799707903
TI Clinical, pathological, and etiologic aspects of acquired dermal melanocytosis.
AU Mizoguchi, Masako (1); Murakami, Fumiko; Ito, Masau; Asano, Mari; Baba, Takako; Kawa, Yoko; Kubota, Yasuo
CS (1) Dep. Dermatology, St. Marianna Univ. Sch. Med., 2-16-1 Sugao, Miyame-Ku, Kawasaki 216 Japan

SO Pigment Cell Research, (1997) Vol. 10, No. 3, pp. 176-183.
ISSN: 0893-5785.
DT Article
LA English
AB To study the pathogenesis of acquired dermal melanocytosis (ADM), we reviewed the clinical, immunohistochemical, and ultrastructural features of 34 cases (female, 33, and male, 1) of ADM. The patients' ages at onset ranged from 8 to 51 years and averaged 26.8+12.7 years. There was a positive family history. Gray-brown macules were mostly recognized on the face. Not only active dermal melanocytes but also non-**pigmented** **c-KIT**- and TRP-2-positive immature melanocytes were detected in the dermis. Taken together those clinical and histological findings, activation of pre-existing immature melanocytes by sunlight, estrogen, and/or progesterone, and some other factors, may be the most likely mode of the development of ADM. Moreover, using cultured murine neural crest cells as a model of **c-KIT**-positive immature melanocytes, we confirmed that endothelin-1, which is produced and secreted by keratinocytes after UV-irradiation, affects melanocytes and accelerated melanogenesis.

L66 ANSWER 20 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:204759 BIOSIS
DN PREV199799503962
TI The effect of recombinant **stem cell factor** on human skin and lung mast cells and basophil leukocytes.
AU Frenz, A. M.; Gibbs, B. F.; Pearce, F. L. (1)
CS (1) University Coll. London, Dep. Chemistry, 20 Gordon St., London WC1H 0AJ UK
SO Inflammation Research, (1997) Vol. 46, No. 2, pp. 35-39.
ISSN: 1023-3830.
DT Article
LA English
AB Recombinant human **stem cell factor** (rhSCF) induced histamine release from human skin and lung mast cells but had no effect on human basophil leukocytes. More importantly, rhSCF enhanced the release of histamine in response to IgE-crosslinking of human mast cells. This potentiation was observed at rhSCF concentrations which induced histamine release, and also at lower concentrations of the ligand which by themselves produced no effect. Very limited potentiation was observed with human basophil leukocytes. The enhancing effect of SCF was unique to IgE-dependent stimulation and when SCF was incubated with the neurotransmitter substance P and the calcium ionophore A23187, no augmentation of histamine release was observed with any of the cell types tested. These findings suggest that endogenous SCF may contribute to the regulation of mast cell function and may hence play a role in diverse allergic and **inflammatory** reactions.

L66 ANSWER 21 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:538552 BIOSIS
DN PREV199699260908
TI Histamine release in intact human skin by monocyte chemoattractant factor-1 RANTES, macrophage **inflammatory** protein-1-alpha, **stem cell factor**, anti-IgE, and codeine as determined by an ex vivo skin microdialysis technique.
AU Petersen, Lars J. (1); Brasso, Klaus; Pryds, Morten; Skov, Per S.
CS (1) Dep. Dermatol., Bispebjerg Hosp., DK-2400 Copenhagen NV Denmark
SO Journal of Allergy and Clinical Immunology, (1996) Vol. 98, No. 4, pp. 790-796.
ISSN: 0091-6749.
DT Article
LA English
AB Background: The chemokines monocyte chemoattractant factor-1, RANTES, and macrophage **inflammatory** protein-1-alpha release histamine from human basophils, as well as rat and mouse mast cells. The purpose of this investigation was to determine whether these chemokines release histamine from human skin mast cells in situ. Methods: A microdialysis technique was

used to measure histamine release in skin. First, the model was validated by using anti-IgE, codeine, and **stem cell factor** (SCF); then the histamine-releasing effects of the chemokines were investigated. A total of 47 skin specimens from 41 donors were investigated. Hollow microdialysis fibers were inserted intradermally, and each fiber was slowly perfused (3 mu-l/min). Anti-IgE, codeine, SCF, or chemokines were injected intradermally above individual fibers, and dialysate was collected at 2-minute intervals for 20 minutes. Each series of investigations comprised five to eight single experiments. Results: Anti-IgE (4 to 4000 U/ml), codeine (0.001 to 1 mg/ml), and SCF (5.4 times (10-11 to 10-8 mol/L)) released histamine in a dose-dependent manner; maximum histamine release was 97 4, 116 3, and 9.5 pmol/20 min, respectively. Monocyte chemoattractant factor-1, RANTES, and macrophage **inflammatory** protein-1-alpha in concentrations of 10-9 to 10-6 mol/L did not release histamine; histamine release by 10-6 mol/L chemokine was less than 0.2 pmol/20 min. None of the chemokines modulated anti-IgE-induced histamine release. In contrast, SCF significantly potentiated anti-IgE-induced histamine release by 33%. All chemokines, but not SCF, released histamine from human basophils. Conclusion: We conclude that the chemokines monocyte chemoattractant factor-1, RANTES, and macrophage **inflammatory** protein-1-alpha. do not release histamine from human skin mast cells.

L66 ANSWER 22 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:509721 BIOSIS
DN PREV199699232077
TI **Stem cell factor** regulates the melanocyte cytoskeleton.
AU Scott, Glynis (1); Liang, Hong; Luthra, Dipika
CS (1) Dep. Dermatol., Univ. Rochester Sch. Med. Dent., 601 Elmwood Ave., Rochester, NY 14642 USA
SO Pigment Cell Research, (1996) Vol. 9, No. 3, pp. 134-141. ISSN: 0893-5785.
DT Article
LA English
AB **Stem cell factor** is a growth factor for normal human melanocytes, that acts through the tyrosine kinase receptor **c-kit**. We have previously demonstrated that **stem cell factor** increases melanocyte adhesion and migration on fibronectin, and regulates integrin protein expression. In this report, we have characterized the effect of **stem cell factor** on the organization of the actin cytoskeleton in human melanocytes attached to fibronectin, and have examined the effect of **stem cell factor** on the phosphorylation of the focal contact protein paxillin and on the expression of the focal contact proteins talin, paxillin, vinculin, and alpha-actinin. Paxillin is a vinculin-binding protein that is a substrate of focal adhesion kinase, a nonreceptor tyrosine kinase, and in its phosphorylated form is believed to stabilize focal contacts. We show that **stem cell factor** induces a rapid increase in actin stress fiber formation in melanocytes, which can be abrogated by genistein, a tyrosine kinase inhibitor, and that **stem cell factor** induces phosphorylation of paxillin on tyrosine residues. In contrast, **stem cell factor** did not regulate expression of any of the four focal contact proteins tested. These findings have implications for the models describing the mechanisms of action of **stem cell factor** on melanocyte adhesion and migration, and suggest that reorganization of the cytoskeleton is a primary effect of **stem cell factor** on human melanocytes.

L66 ANSWER 23 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:505740 BIOSIS
DN PREV199699228096
TI Foetal human melanocytes: In situ detection, in vitro culture and differentiation characteristics at 6-11 weeks EGA.

AU Le Poole, I. Caroline (1); Van Den Wijngaard, Rene M. J. G. J.; Verkruissen, Ronald P.; Lamers, Wout H.; Troost, Dirk; Westerhof, Wiete; Das, Pranab K.
CS (1) Dep. Dermatol. Pathol., AMC/Amsterdam Univ., Meibergdreef 9, 1105 AZ Amsterdam Netherlands
SO Pigment Cell Research, (1996) Vol. 9, No. 3, pp. 126-133.
ISSN: 0893-5785.
DT Article
LA English
AB In vivo, melanocytes were detected in epidermis from human tissue of 6.5 weeks estimated gestational age (EGA) and older. We have successfully established melanocyte monocultures from tissue of 9 to 10 weeks EGA. To our knowledge, this is the first report on physiology of human foetal melanocytes in monoculture. In culture, such melanocytes retained foetal characteristics. Proliferation rates noted were markedly higher (approximately 2.7-fold) when compared to those in cultures of neonatal melanocytes. Moreover, when analyzing cellular phenotypes by markers for cells of the melanocytic lineage, foetal cells isolated from tissue of 9 weeks EGA reproducibly showed expression of the high molecular weight (HMW) antigen and **c-kit** to an extent intermediate to that found in neonatal melanocytes and M14 melanoma cells. Such differential expression was not observed if cells were isolated from tissue of 10 weeks EGA, indicating that the foetal environment provides essential differentiation stimuli during the 10th week of gestation. Moreover, these results are supportive of the theory that malignant transformation involves a process of dedifferentiation. In all, human foetal melanocyte culture provides a useful model to investigate **pigment** cell differentiation.

L66 ANSWER 24 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:440012 BIOSIS
DN PREV199699162368
TI Biology and pathophysiology of leukotrienes.
AU Denzlinger, Claudio
CS Med. Klinik III, Klinikum Grosshadern, Ludwig-Maximilians Univ. Muenchen, 81377 Muenchen Germany
SO Critical Reviews in Oncology-Hematology, (1996) Vol. 23, No. 3, pp. 167-223.
ISSN: 1040-8428.
DT General Review
LA English

L66 ANSWER 25 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:439263 BIOSIS
DN PREV199699152869
TI Effects of basophil-priming and stimulating cytokines of histamine release from isolated human skin mast cells.
AU Nitschke, Martin; Sohn, Karen; Dieckmann, Detlef; Gibbs, Berhard F.; Wolff, Helmut H.; Amon, Ulrich (1)
CS (1) Dep. Dermatol., Med. Univ. Luebeck, Ratzeburger Allee 160, D-23538 Luebeck Germany
SO Archives of Dermatological Research, (1996) Vol. 288, No. 8, pp. 463-468.
ISSN: 0340-3696.
DT Article
LA English
AB Cell priming and stimulation of different cytokines (which include chemokines and growth factors) are typical features of human basophils. Recently, it has been shown that the macrophage chemotactic protein-1 (MCP-1), RANTES and macrophage **inflammatory** protein-1-alpha (MIP-1-alpha) are potent direct secretagogues for human basophils and that interleukin-3 (IL-3), IL-5 and granulocyte/macrophage colony-stimulating factor (GM-CSF) are priming factors for subsequent potentiation of mediator release from basophils induced by different stimuli. This observation may be clinically important for the activation and recruitment of **inflammatory** cells in different immune responses of the skin (e.g. late-phase reactions). The aim of the present study was to

investigate whether cytokines and chemokines are also capable of priming or stimulating isolated human skin mast cells (SMC). SMC were either stimulated directly with the cytokines alone or preincubated with these factors for 10 min before being activated with suboptimal concentrations of anti-IgE, A23187 or substance P. IL-3, IL-5, GM-CSF, platelet factor-4 (PF-4), IL-8, MCP-1 and MIP-1-alpha (each at concentrations of 1 ng/ml to 1 mu-g/ml, log steps) did not significantly modulate histamine release from SMC induced by the three different secretagogues. RANTES exhibited a weak but significant potentiating effect on IgE-mediated activation. **Stem cell factor** (SCF) as a positive control was able to prime mast cell histamine release strongly. In addition, PF-4, MCP-1, RANTES and MIP-1a were incapable of inducing direct histamine release from SMC. In experiments with isolated human peripheral basophils, however, we observed potent Fc-epsilon-RI-mediated priming effects evoked through IL-3, IL-5, and GM-CSF. We conclude that SMC derived from healthy donors are not targets of (immuno)modulatory factors that prime or stimulate basophils.

L66 ANSWER 26 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:434712 BIOSIS
DN PREV199699148318
TI Ectopic **c-kit** expression affects the fate of melanocyte precursors in patch mutant embryos.
AU Wehrle-Haller, Bernhard; Morrison-Graham, Kathleen; Weston, James A.
CS Inst. Neuroscience, 1254 University of Oregon, Eugene, OR 97403-1254 USA
SO Developmental Biology, (1996) Vol. 177, No. 2, pp. 463-474. ISSN: 0012-1606.
DT Article
LA English
AB The Patch (Ph) mutation in the mouse, a deletion that includes the gene for PDGFR-alpha, is a recessive lethal that exhibits a dominant **pigment** phenotype in heterozygotes. To assess whether the Ph mutation acts cell-autonomously or nonautonomously on melanocyte development, we have examined the melanogenic potential of neural crest populations from normal and mutant crest cells in vitro and the pattern of dispersal and survival of melanocyte precursors (MPs) in vivo. We report that trunk neural crest cells from homozygous Ph embryos give rise to **pigmented** melanocytes in vitro in response to Steel factor (SIF). In vivo, homozygous Ph embryos contain a subpopulation of crest-derived cells that express **c-kit** and tyrosinase-related protein-2 characteristic of MPs. These cells begin to migrate normally on the lateral crest migration pathway, but then fail to disperse in the dermal mesenchyme and subsequently disappear. Although dermal mesenchyme is adversely affected in Ph homozygotes, SIF mRNA expression by the cells of the dermatome is normal in Ph embryos when neural crest-derived MPs start to migrate on the lateral pathway. In contrast, mRNA for the SIF receptor, **c-kit**, was observed to be ectopically expressed in somites and lateral mesenchyme in embryos carrying the Ph mutation. Based on this ectopic expression of **c-kit** in Ph mutant embryos, and the observed distribution of SIF protein in normal and mutant embryos, we suggest that competition for limited amounts of SIF localized on the lateral neural crest migration pathway alters melanocyte dispersal and survival.

L66 ANSWER 27 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:367443 BIOSIS
DN PREV199699089799
TI Recombinant human **stem cell factor** (Kit Ligand) promotes human mast cell and melanocyte hyperplasia and functional activation in vivo.
AU Costa, John J.; Demetri, George D.; Harrist, Terence J.; Dvorak, Ann M.; Hayes, Daniel F.; Merica, Elizabeth A.; Menchaca, Dora M.; Gringeri, Anthony J.; Schwartz, Lawrence B.; Galli, Stephen J. (1)
CS (1) Div. Experimental Pathol., Dep. Pathology, RN227, Beth Israel Hosp., 330 Brookline Avenue, Boston, MA 02215 USA
SO Journal of Experimental Medicine, (1996) Vol. 183, No. 6, pp. 2681-2686.

ISSN: 0022-1007.
DT Article
LA English
AB **Stem cell factor** (SCF), also known as mast cell growth factor, **kit** ligand, and Steel factor, is the ligand for the tyrosine kinase receptor (SCFR) that is encoded by the **c -kit proto-oncogene**. We analyzed the effects of recombinant human SCF (r-hSCF, 5-50 mu-g/kg/day, injected subcutaneously) on mast cells and melanocytes in a phase I study of 10 patients with advanced breast carcinoma. A wheal and flare reaction developed at each r-hSCF injection site; by electron microscopy, most dermal mast cells at these sites exhibited extensive, anaphylactic-type degranulation. A 14-d course of r-hSCF significantly increased dermal mast cell density at sites distant to those injected with the cytokine and also increased both urinary levels of the major histamine metabolite, methyl-histamine, and serum levels of mast cell alpha-tryptase. Five subjects developed areas of persistent **hyperpigmentation** at r-hSCF injection sites; by light microscopy, these sites exhibited markedly increased epidermal melanization and increased numbers of melanocytes. The demonstration that r-hSCF can promote both the hyperplasia and the functional activation of human mast cells and melanocytes in vivo has implications for our understanding of the role of endogenous SCF in health and disease. These findings also indicate that the interaction between SCF and its receptor represents a potential therapeutic target for regulating the numbers and functional activity of both mast cells and cutaneous melanocytes.

L66 ANSWER 28 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:366006 BIOSIS
DN PREV199699088362
TI Dermal papilla cells derived from beard hair follicles secrete more **stem cell factor** (SCF) in culture than scalp cells or dermal fibroblasts.
AU Hibberts, Nigel A.; Messenger, Andrew G.; Randall, Valerie A. (1)
CS (1) Dep. Biomedical Sci., Univ. Bradford, Bradford UK
SO Biochemical and Biophysical Research Communications, (1996) Vol. 222, No. 2, pp. 401-405.
ISSN: 0006-291X.
DT Article
LA English
AB As **stem cell factor** (SCF) and its receptor, **c-kit**, are involved in hair **pigmentation**, SCF is probably produced in the skin, possibly by the regulatory follicular dermal papilla. Since androgens often alter the type and color of hair, probably via the dermal papilla, they may regulate its SCF production. SCF produced by beard and non-balding scalp dermal papilla cells in the presence, or absence, of 10nM testosterone was assayed by ELISA. After 24h, beard cells produced significantly ($p = 0.001$) moe SCF than scalp cells, while beard and scalp fibroblasts secreted significantly ($p = 0.04$) less SCF. Testosterone in vitro had no effect on SCF secretion. These results support the hypotheses that the dermal papilla is a local source of SCF in hair follicles and that androgens would alter SCF production only at specific points of the hair cycle.

L66 ANSWER 29 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:264913 BIOSIS
DN PREV199698821042
TI Distinct stages of melanocyte differentiation revealed by analysis of nonuniform **pigmentation** patterns.
AU Yoshida, Hisahiro (1); Kunisada, Takahiro; Kusakabe, Moriaki; Nishikawa, Satomi; Nishikawa, Shin-Ichi
CS (1) Dep. Mol. Genet., Fac. Med., Kyoto University, Shogoin Kawaharacho 53, Sakyo-ku, Kyoto 606-01 Japan
SO Development (Cambridge), (1996) Vol. 122, No. 4, pp. 1207-1214.
ISSN: 0950-1991.
DT Article

LA English
AB The injection of an antagonistic anti-murine **c-kit** monoclonal antibody ACK2 during mouse embryonic development produced three distinctive **pigmentation** patterns on the coat of the offspring. Pattern 1 consisted of **pigmentation** in craniofacial and caudal regions and was induced by an ACK2 injection between 9.5 and 11.5 days post coitum (dpc). In pattern 2, the entire coat was **unpigmented** and was induced by the injection at around 13.0 dpc. Pattern 3 consisted of **pigmented** patches spreading ventrolaterally from the dorsoanterior trunk regions towards the anterior and posterior directions and it was induced by ACK2 administered at 14.5-15.0 dpc. We investigated the embryological basis of these nonuniform **pigmentation** patterns to elucidate the process of melanoblast differentiation between lineage commitment and colonization into developing hair follicles. The results showed the following. (1) Melanocyte differentiation at the embryonic stage from 10.5 to 12.5 dpc progresses in a spatially nonuniform fashion, being faster in the craniofacial and caudal regions than in the trunk; pattern 1 reflects this. (2) Melanoblasts are activated to proliferate synchronously upon entering into the epidermis; pattern 2 correlates with this process. (3) **c-kit** functions as a survival signal for proliferating melanoblasts in the epidermis. (4) The melanoblasts that enter developing hair follicles can survive without a **c-kit** signal; pattern 3 essentially represents the hair follicles colonized by these cells. Analysis of the melanoblast distribution of ls/ls embryos that bear a loss-of-function mutation in the endothelin 3 gene suggested that endothelin 3 is required for early melanoblast differentiation before entering into the epidermis, whereas proliferation in the epidermis takes place without this molecule. Based on these data, we propose 4 distinct steps of embryonic melanocyte differentiation: (1) migration in the dermis, which requires both **c-kit** and endothelin 3; (2) a stage before epidermal entry that is resistant to anti-**c-kit** mAb; (3) cell proliferation after entering the epidermal layer, which requires **c-kit** and endothelin receptor B but not endothelin 3 and (4) integration into developing hair follicles, which renders melanoblasts resistant to anti-**c-kit** mAb. Thus, melanoblast differentiation proceeds by alternately repeating **c-kit**-dependent and **c-kit**-independent stages and **c-kit** functions as a survival factor for the proliferating melanoblasts.

L66 ANSWER 30 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:216809 BIOSIS
DN PREV199698772938
TI Multiple actions of **stem cell factor** in neural crest cell differentiation in vitro.
AU Langtimm-Sedlak, Carol J.; Schroeder, Brett; Saskowski, Jeanette L.; Carnahan, Josette F.; Sieber-Blum, Maya (1)
CS (1) Dep. Cellular Biol. Anatomy, Med. Coll. Wisconsin, Milwaukee, WI 53226 USA
SO Developmental Biology, (1996) Vol. 174, No. 2, pp. 345-359. ISSN: 0012-1606.
DT Article
LA English
AB The neural crest is a transient tissue of the vertebrate embryo that gives rise to most primary sensory neurons and **pigment** cells in the adult organism, among other cell types and tissues. Many neural crest cells are pluripotent in the sense that their progeny can generate more than one phenotype. The presence of pluripotent neural crest cell-derived cells at sites of terminal differentiation suggests that location-specific cues from the embryonic environment, such as growth factors, are involved in directing their survival, proliferation, and cell type specification. We have therefore examined the influences of one pertinent growth factor, **stem cell factor** (SCF), on neural crest cell development by in vitro colony assay in a serum-free culture medium. SCF showed three major effects. (1) SCF is trophic for early neural crest

cells, that is, either pluripotent cells and/or their more mature progeny. This effect occurs only if SCF is present throughout the culture period, and it is not observed when a neurotrophin is present in addition to SCF. (2) More colonies contain sensory neuron precursors in the presence of SCF. This effect is neutralized by NGF and neurotrophin-3 (NT-3), but not by brain-derived neurotrophic factor (BDNF). (3) The combination of SCF and any neurotrophin tested (NGF, BDNF, NT-3) is trophic for melanogenic cells, whereas SCF alone does not detectably affect melanogenesis. This suggests either that both types of factor are required for melanotrophic action or that melanogenic cells become dependent on neurotrophins after exposure to SCF. Our observation that SCF is required during the first half of the culture period only, and NGF during the second half only, indicates the latter possibility. Whereas coat color changes in the mouse mutants W (**c-kit** defect) and Steel (SCF defect) and several in vivo and in vitro studies by other investigators have shown previously that SCF is melanotrophic, they also indicated the requirement of an additional factor, or factors, in melanogenesis. Our data suggest that SCF affects neural crest cell development at multiple levels and that survival of melanogenic cells is mediated by a combination of SCF and a neurotrophin, rather than by SCF alone.

L66 ANSWER 31 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:190176 BIOSIS
DN PREV199698746305
TI **C-KIT** receptor expression in cutaneous malignant melanoma and benign melanocytic naevi.
AU Ohashi, A.; Funasaka, Y. (1); Ueda, M.; Ichihashi, M.
CS (1) Dep. Dermatology, Kobe Univ. Sch. Med., 5-1 Kusunoki-cho 7-chome, Chuo-ku, Kobe 650 Japan
SO Melanoma Research, (1996) Vol. 6, No. 1, pp. 25-30. ISSN: 0960-8931.
DT Article
LA English
AB To investigate the role of **c-KIT** receptor in melanocytic tumour development and progression, we analysed the expression and localization of **c-KIT** by immunohistochemistry and Western blotting. In contrast to the positive staining shown by melanocytes and naevus cells in the epidermis of common naevi (n=20), all dysplastic naevi (n = 13) were negative, as were dermal melanocytic cells of blue naevi (n = 4) and common naevi (n = 26). Three out of four superficial spreading melanomas lost **c-KIT** expression both in the epidermal and dermal parts, while nodular melanomas showed no expression of **c-KIT** except in partially positive cells, and six out of seven metastatic melanomas were negative. In acral lentiginous melanomas (n = 8), in contrast to other types of melanoma, all cases with melanoma cells growing basally in the epidermis showed strong **c-KIT** positivity, but melanoma cells growing at the upper layers of the epidermis and vertically into the dermis lost **c-KIT** expression. Using the Western blot method on cultured **pigment** cells, human epidermal melanocytes, junctional naevus cells and one out of three metastatic melanoma cell lines showed 125 and 145 kDa bands corresponding to **c-KIT**, whereas dermal naevus cells did not. These results suggest that dysplastic naevi are distinct from ordinary naevi in terms of **c-KIT** expression and that basally growing cells in acral lentigenous melanomas could be at an initial stage of tumour progression, before **c-KIT** loss occurs.

L66 ANSWER 32 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:108290 BIOSIS
DN PREV199698680425
TI Exogenous but not endogenous substance P releases histamine from isolated human skin fragments.
AU Tausk, F. (1); Undem, B.
CS (1) Dep. Dermatol., 6th Fl., Johns Hopkins Outpatient Cent., 601 N. Caroline St., Baltimore, MD 21287-0900 USA

SO Neuropeptides, (1995) Vol. 29, No. 6, pp. 351-355.
ISSN: 0143-4179.
DT Article
LA English
AB Neuropeptides such as substance P are released from nerve terminals following the stimulation of sensory fibers, and are thought to participate in neurogenic **inflammation** in the skin; it is often speculated that mast cell activation is an intermediate step in this process. In the present study we addressed this hypothesis using freshly obtained skin explants derived from human neonatal foreskins or adult skin resections. The results demonstrate that when substance P is released from human skin by incubation in the presence of capsaicin (10-5 M), no histamine is released from human isolated skin fragments. In each experiment human recombinant **stem cell factor** and/or exogenously applied substance P effectively evoked histamine release from the explants, attesting to the viability of the mast cells in the preparation. The concentrations of exogenously applied substance P required to elicit histamine release, however, were large (gt 10 mu-M). These results indicate that substance P released from cutaneous sensory nerve fibers does not reach sufficient concentrations in the skin to degranulate mast cells. These data support the hypothesis that the vascular effects of neurogenic **inflammation** occur independently of mast cell activation.

L66 ANSWER 33 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:108255 BIOSIS
DN PREV199698680390
TI Granulocyte/macrophage colony-stimulating factor is an intrinsic keratinocyte-derived growth factor for human melanocytes in UVA-induced melanosis.
AU Imokawa, Genji (1); Yada, Yukihiro; Kimura, Mitsutoshi; Morisaki, Naoko
CS (1) Inst. Fundamental Res., Kao Corporation, 2606 Akabane, Ichikaimachi, Haga, Tochigi 321-34 Japan
SO Biochemical Journal, (1996) Vol. 313, No. 2, pp. 625-631.
ISSN: 0264-6021.
DT Article
LA English
AB Recently we demonstrated that endothelins secreted from human keratinocytes act as intrinsic mitogens and melanogens for human melanocytes in UVB-induced melanosis. We show here that UVA-induced melanosis is associated with other keratinocyte-derived growth factors, secretion of which is specifically stimulated after exposure of human keratinocytes to UVA. Medium conditioned by UVA-exposed human keratinocytes elicited a significant increase in DNA synthesis by cultured human melanocytes in a UVA dose-dependent manner. Analysis of endothelin-1 and interleukin (IL)-1-alpha in the conditioned medium by ELISA, both of which are major keratinocyte-derived cytokines involved in UVB-associated melanocyte activation, revealed that UVA exposure did not cause human keratinocytes to stimulate the secretion of the two cytokines. In contrast, the levels of several other cytokines such as IL-6, IL-8 and granulocyte/macrophage colony-stimulating factor (GM-CSF) were significantly increased in the conditioned medium of human keratinocytes after exposure to UVA at a dose of 1.0 J/cm-2. The gel chromatographic profile of UVA-exposed keratinocyte-conditioned medium demonstrated that there were two factors (P-1 and P-2) with molecular masses of approx. 20 and 1 kDa respectively that stimulate DNA synthesis in human melanocytes, and the larger species (P-1) also increased melanization as assessed by (14C)thiouracil incorporation. Quantitative analysis of cytokines in chromatographic fractions by ELISA revealed the P-1 fraction to be consistent with the molecular mass profile of GM-CSF. Furthermore the stimulatory effect of the P-1 fraction on DNA synthesis in human melanocytes was neutralized by antibodies to GM-CSF, but not to basic fibroblast growth factor or **stem cell factor** . Binding and proliferation assays with recombinant GM-CSF demonstrated that human melanocytes possess specific binding sites for GM-CSF (K-d 2.11 nM; binding sites, 2.5-3.5 times 10-4 per cell), and recombinant GM-CSF at

concentrations of more than 10 nM significantly stimulated DNA synthesis and melanization. These findings suggest that GM-CSF secreted by keratinocytes plays an essential role in the maintenance of melanocyte proliferation and UVA-induced **pigmentation** in the epidermis.

L66 ANSWER 34 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:20896 BIOSIS
DN PREV199698593031
TI Physical mapping of the Tec and Gabrb1 loci reveals that the W-sh mutation on mouse chromosome 5 is associated with an inversion.
AU Nagle, Deborah L.; Kozak, Christine A.; Mano, Hiroyuki; Chapman, Verne M.; Bucan, Maja (1)
CS (1) Dep. Psychiatry, Univ. Pennsylvania, 415 Curie Blvd., Philadelphia, PA 19104 USA
SO Human Molecular Genetics, (1995) Vol. 4, No. 11, pp. 2073-2079. ISSN: 0964-6906.
DT Article
LA English
AB In the mouse, mutations in the **c-Kit proto-oncogene**, a member of the receptor tyrosine kinase (RTK) gene family, have pleiotropic effects on hematopoiesis, **pigmentation** and fertility (dominant spotting, W). However, in the W-sh allele the defect is confined to abnormal **pigmentation** caused by the disruption of 5' regulatory sequences of **Kit** leaving an intact structural gene. In this report, the previously published physical map around the Pdgfra-**Kit**-Flk1 RTK loci is extended by mapping the loci encoding the GABA-A (gamma-aminobutyric acid) receptor subunit beta 1, Gabrb1 and a cytoplasmic kinase (Tec) 3 Mb proximal to **Kit** PFGE analysis of the wild-type (C57BL/6J) chromosome demonstrates the following gene order: cenGabrb1-Tec-Pdgfra-**Kit**, whereas the analysis of W-sh/ W-sh DNA is consistent with the order: cen-Gabrb1-Pdgfra-Tec-**Kit**. This altered physical map can be explained by an inversion on the W-sh chromosome located proximally to the **Kit** locus and spanning the 2.8 Mb Pdgfra-Tec chromosomal segment. This high resolution physical mapping study identifies large DNA fragments that span the two inversion breakpoints and potentially carry **Kit** upstream regulatory elements involved in the control of **Kit** expression during embryonic development.

L66 ANSWER 35 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:535949 BIOSIS
DN PREV199598550249
TI Coordinated mRNA expression of **c-Kit** with tyrosinase and TRP-1 in melanin **pigmentation** of normal and malignant human melanocytes and transient activation of tyrosinase by Kit/SCF-R.
AU Luo, D.; Chen, H.; Searles, G.; Jimbow, K. (1)
CS (1) Dermatol. and Cutaneous Sci., Fac. Med., 260G Heritage Med. Res. Cent., Unv. Alberta, Edmonton, AB T6G 2S2 Canada
SO Melanoma Research, (1995) Vol. 5, No. 5, pp. 303-309. ISSN: 0960-8931.
DT Article
LA English
AB The **proto-oncogene c-Kit** encodes a membrane receptor protein with intrinsic tyrosine kinase activity. Activation of **c-Kit** induces cell proliferation, differentiation or migration among different cell types. The present study provides evidence that **c-Kit** plays an important role in the cell differentiation rather than in cell proliferation in **pigment** cells. We found that normal human melanocytes and a limited number of melanoma cells, e.g. WM35, WM39 and G361 cell lines, expressed the **c-Kit** gene together with tyrosinase and TRP-1 genes. When exposed to alpha-melanocyte stimulating hormone, these three cell lines also showed an increased tyrosinase (dopa-oxidase) activity. By incubating these cells with 20 ng/ml of **stem cell factor** (SCF) which is a ligand of **c-Kit** receptor, we found a transient increase of tyrosinase activity

2-4 h post-incubation, indicating an early response of tyrosinase activation, either by elevating tyrosinase protein expression or by tyrosinase protein modification (e.g. phosphorylation). However, Western blot analysis using anti-tyrosinase antibody suggested that there was no change of tyrosinase protein expression between SCF-treated and non-treated cells. We therefore suggest that protein modulation of tyrosinase (e.g. phosphorylation) plays an important role in **c-Kit**-induced melanogenesis.

L66 ANSWER 36 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:533034 BIOSIS
DN PREV199598547334
TI Phenotypic reversions at the W/Kit locus mediated by mitotic recombination in mice.
AU De Sepulveda, Paulo; Guenet, Jean-Louis; Panthier, Jean-Jacques (1)
CS (1) URA-INRA Genetique Mol., Ecole Natl. Vet. Alfort, 7 ave. du General-de-Gaulle, 94704 Maisons-Alfort Cedex France
SO Molecular and Cellular Biology, (1995) Vol. 15, No. 11, pp. 5898-5905. ISSN: 0270-7306.
DT Article
LA English
AB The mouse W locus encodes **Kit**, the receptor tyrosine kinase for **stem cell factor** (SCF). **Kit** is required for several developmental processes, including the proliferation and survival of melanoblasts. Because of the nearly complete failure of W-rio/+ melanoblasts to colonize the skin, the coats of W-rio/+ mice are characterized by a majority of white hairs interspersed among **pigmented** hairs, giving a roan effect. However, 3.6% of W-rio/+ mice exhibit phenotypic reversions, i.e., spots of wild-type color on their coats with an otherwise mutant phenotype. Melanocyte cell lines were derived from each of six independent reversion spots on the skin of (C57BL/6 times DBA/2)F-1 W-rio/+ mice. All six melanocyte cell lines exhibited the general characteristics common to normal, nonimmortal mouse melanocytes. Of these, three revertant cell lines had lost the dominant-negative W-rio allele following mitotic recombination between the centromere and the W locus. One of the cell lines remained W-rio/+ but showed (i) stimulation in response to SCF and (ii) increased **Kit** expression, suggesting that the W-rio mutation can be rescued by increased endogenous expression of the **c-kit proto-oncogene**. Finally, two cell lines showed no detectable genetic change at the W/**Kit** locus and failed to respond to SCF stimulation in vitro. These results demonstrate that mitotic recombination can create large patches of wild-type hair on the coats of W-rio/+ mutant mice. This shows that mitotic recombination occurs spontaneously in normal healthy tissue in vivo. Moreover, these experiments confirm that other mechanisms, not associated with loss of heterozygosity, may account for the coat color reversion phenotype.

L66 ANSWER 37 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:503215 BIOSIS
DN PREV199598526765
TI Human recombinant **stem-cell factor** induces melanocytic hyperplasia in susceptible patients.
AU Grichnik, James M. (1); Crawford, Jeffrey; Jimenez, Francisco; Kurtzberg, Joanne; Buchanan, Mark; Blackwell, Susan; Clark, Robert E.; Hitchcock, Michael G.
CS (1) Div. Dermatol., Dep. Med., Duke Univ. Med. Cent., Durham, NC 27710 USA
SO Journal of the American Academy of Dermatology, (1995) Vol. 33, No. 4, pp. 577-583. ISSN: 0190-9622.
DT Article
LA English
AB Background: Recombinant human **stem-cell factor** (SCF), a cytokine acting on hematopoietic progenitor cells, has potential for the treatment of several hematologic and oncologic disorders. In a hematology-oncology phase I trial of SCF, several patients had cutaneous

hyperpigmentation at the SCF subcutaneous injection sites. Objective: Our purpose was to investigate the pathogenesis of this **hyperpigmentation** phenomenon. Methods: Skin biopsy specimens were obtained before, at the completion of, and after SCF therapy and were processed for histology, immunohistology, and electron microscopy. Results: Skin at the site of SCF injection had an increased number of melanocytes, increased melanocytic dendrite extension, and melanin as compared with noninjected tissue. Immunohistochemical stains revealed an increase in staining with melanocyte-specific monoclonal antibodies HMB-45 and NKI/beteb, and a monoclonal antibody to the receptor for SCF, **c-kit**. Conclusion: Subcutaneous injection of SCF results in hyperplasia of melanocytes. SCF may be useful in the treatment of melanocytopenic disorders, but caution may be necessary in patients with disorders of melanocyte proliferation.

L66 ANSWER 38 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:440230 BIOSIS
DN PREV199598454530
TI Expression of **stem cell factor** in cutaneous mastocytosis.
AU Hamann, K.; Haas, N.; Grabbe, J.; Czarnetzki, B. M. (1)
CS (1) Dep. Dermatol., UKRV, Freie Univ., Augustenburgerplatz 1, D-13344 Berlin Germany
SO British Journal of Dermatology, (1995) Vol. 133, No. 2, pp. 203-208. ISSN: 0007-0963.
DT Article
LA English
AB **Stem cell factor** has recently been identified as a potent growth factor for bone marrow stem cells, melanocytes and mast cells. In order to evaluate its possible role in human mastocytosis, skin lesions from 13 patients with urticaria **pigmentosa** and five patients with mastocytomas, and normal skin specimens from five healthy donors were studied by immunohistochemistry, using polyclonal and monoclonal (hkl-12) antibodies against **stem cell factor**, and a monoclonal antibody (YB5.B8) against its receptor, the **c-kit proto-oncogene** product. **Stem cell factor** expression was noted in all sections studied, with an equal distribution pattern for both antibodies, but a weaker intensity with the hkl-12 reagent. Cytoplasmic staining was noted in keratinocytes, Langerhans cells, sweat gland ductal lining cells, mast cells, endothelial cells and spindle-shaped dermal stromal cells. An intense, diffusely granular reaction pattern was noted in all cells, except for a sparse, coarsely granular pattern in mast cells and stromal cells. In urticaria **pigmentosa**, staining was weaker in keratinocytes, but more prominent in Langerhans cells. In all sections, toluidine blue-positive mast cells and TA 99-positive basal epidermal melanocytes were the only cells to react with the **c-kit** antibody. Mastocytomas and urticaria **pigmentosa** lesions thus exhibit different patterns of **stem cell factor** expression. However, a possible pathogenetic role of this factor in mastocytosis remains to be determined.

L66 ANSWER 39 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:346195 BIOSIS
DN PREV199598360495
TI Steel factor directs melanocyte development in vitro through selective regulation of the number of **c-kit**+ progenitors.
AU Reid, Kate; Nishikawa, Shin-Ichi; Bartlett, Perry F.; Murphy, Mark (1)
CS (1) Walter Eliza Hall Inst. Med., Res., Post Office, Royal Melbourne Hosp., Parkville, VIC 3050 Australia
SO Developmental Biology, (1995) Vol. 169, No. 2, pp. 568-579. ISSN: 0012-1606.
DT Article
LA English
AB Studies of mice containing mutations in the genes for a receptor tyrosine

kinase, **c-kit**, or its cognate ligand, Steel factor (SLF), establish that this signaling pathway is required for the development of melanocytes from their precursors in the embryonic neural crest (NC). In order to define the mechanism of this requirement, we have labeled cells expressing **c-kit** with an anti-**c-kit** antibody (ACK2) and studied the action of SLF on these cells in cultures of murine trunk NC. **c-kit** positive (**c-kit**+) cells first appeared after 2 days in culture and were morphologically indistinguishable from other NC cells. These cells subsequently expressed tyrosinase-related protein, an early marker for the melanocyte lineage, and became **pigmented** in the presence of a phorbol ester. Further, elimination of the **c-kit**+ population, by incubating the cultures in ACK2, resulted in the ablation of the melanocyte population, but had no effect on the generation of other neural crest derivatives. These data indicate that **c-kit**+ cells arising from the neural crest are melanocyte progenitors. The addition of SLF to these cultures stimulated an increase in the number of **c-kit**+ cells, and further studies indicated that SLF acts as both a survival and a proliferative factor for **c-kit**+ cells. These findings provide a mechanism of regulation of melanocyte development, whereby **c-kit** is exclusively expressed by melanocyte progenitors within the neural crest precursor population, and subsequent survival and proliferation of these progenitors is regulated by SLF.

L66 ANSWER 40 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:346159 BIOSIS
DN PREV199598360459
TI Human **piebaldism**: Relationship between phenotype and site of kit gene mutation.
AU Ward, K. A. (1); Moss, C. (1); Sanders, D. S. A.
CS (1) Dep. Dermatol., General Hosp., Steelhouse Lane, Birmingham B4 6NH UK
SO British Journal of Dermatology, (1995) Vol. 132, No. 6, pp. 929-935. ISSN: 0007-0963.
DT Article
LA English
AB Human piebaldism is a rare autosomal dominant disorder characterized by congenital **depigmented** patches of skin and hair. Piebaldism results from mutations of the **kit proto-oncogene**, which encodes a cell-surface receptor, tyrosine kinase, whose ligand is the stem/mast cell growth factor. We report four unrelated patients with piebaldism and consider the variations in phenotype in relation to the site of the **kit** gene mutation.

L66 ANSWER 41 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:299475 BIOSIS
DN PREV199598313775
TI A cloned, immortal line of murine melanoblasts inducible to differentiate to melanocytes.
AU Sviderskaya, Elena V.; Wakeling, William F.; Bennett, Dorothy C. (1)
CS (1) St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE UK
SO Development (Cambridge), (1995) Vol. 121, No. 5, pp. 1547-1557. ISSN: 0950-1991.
DT Article
LA English
AB Cultures of differentiated melanocytes can readily be grown from the dissociated epidermis of neonatal mice, and immortal cell lines often develop from these. However, the first cells that grow and transiently dominate the cultures, while similar to melanocytes, are **unpigmented**. These have been shown to be precursors of melanocytes and may be termed melanoblasts. Under our previous standard culture conditions, involving the use of keratinocyte feeder cells, foetal calf serum, the phorbol ester 12-O-tetradecanoyl phorbol acetate (TPA) and cholera toxin, all the melanoblasts spontaneously differentiated to **pigmented** melanocytes within about 3 weeks. We now describe some

factors affecting the proliferation and differentiation of diploid murine melanoblasts in the presence of serum. Murine **stem cell factor**/steel factor (SCF), basic fibroblast growth factor (bFGF) and murine leukaemia inhibitory factor/differentiation-inhibiting activity (LIF/DIA) all increased melanoblast numbers. SCF and LIF also slightly inhibited melanoblast differentiation, while cholera toxin and TPA promoted differentiation. Using some of these findings, and by regular replacement of keratinocyte or fibroblastoid feeder cells, we have established a clonal line of immortal murine melanoblasts, 'melb-a'. These cells express tyrosinase-related protein-2 but not, in general, tyrosinase. They can be induced to differentiate irreversibly to functional melanocytes (also proliferative and immortal) by plating in the absence of feeder cells. Thus a new immortal melanocyte line, 'melan-a2', has also been produced.

L66 ANSWER 42 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:295874 BIOSIS
DN PREV199598310174
TI Steel and **c-kit** in the development of avian melanocytes: A study of normally **pigmented** birds and of the **hyperpigmented** mutant silky fowl.
AU Lecoin, Laure; Lahav, Ronit; Martin, Francis H.; Teillet, Marie-Aimee; Le Gouarin, Nicole M. (1)
CS (1) Inst. d'Embryologie Cellulaire et Molecularie du CNRS et du College de FRA, 49 bis Ave. de la Belle Gabrielle, 94736 Nogentsur-Marne Cedex France
SO Developmental Dynamics, (1995) Vol. 203, No. 1, pp. 106-118. ISSN: 1058-8388.
DT Article
LA English
AB We describe here the expression of **c-kit** and Steel (Sl) genes during the development of melanocytes in normally **pigmented** strains of chick and quail compared to **unpigmented** (White Leghorn) and **hyperpigmented** (Silky Fowl) strains of chickens. By using the quail/chick chimera system, we found that the neural crest cells, which migrate dorso-laterally in the subectodermal mesenchyme to give rise to the melanocytes, express **c-kit** as early as E4, that is about 2 days after they have left the neural primordium. The Sl gene is expressed from E4 onward in the epidermis but not at all in the dermis at any developmental stage. As feather buds develop, SI mRNA becomes restricted to the apical region of the feather filaments. During formation of the barbs and barbules of the down feather, production of the Steel factor is restricted to the external epidermal cells of the barbules. The cell bodies of the **c-kit**-positive melanocytes are then located in the internal border of the epidermal ridges and extend their processes toward the source of the Steel factor. We propose that the spatial restriction of Sl gene activity at that stage accounts for the morphology of the melanocytes and their vectorial secretion of melanin to the external barbule cells. As a whole, these results show that during skin development **c-kit** positive cells are present in the Steel factor-producing areas at the time when melanoblasts proliferate and differentiate. Interestingly, in the mouse, previous studies showed that the Sl gene is activated in the dermis where melanoblasts undergo most of their expansion (Nishikawa et al. (1991) EMBO J. 10:2111-2118). In the **unpigmented** and **hyperpigmented** mutants that we studied, expression of the St message, as judged quantitatively in Northern blots (for the SF embryos) or spatially by in situ hybridization, is similar to that observed in normal birds. In SF embryos the **c-kit** expressing melanoblasts migrate initially in the dorso-lateral migration pathway as in normal birds. However their number increases considerably in the dermis from E5 onward. From E7, they invade mesodermally derived organs that do not express the Sl gene. This suggests that another, still unknown, factor(s) is responsible for the survival, the proliferation, and the extensive spreading of melanocytic cells within the mesoderm of this mutant.

L66 ANSWER 43 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:264022 BIOSIS
DN PREV199598278322
TI The W-sh and Ph mutations affect the **c-kit** expression profile: -kit misexpression in embryogenesis impairs melanogenesis in W-sh and Ph mutant mice.
AU Duttlinger, Regina; Manova, Katia; Berrozpe, Georgina; Chu, Tang-Yang; Deleon, Victor; Timokhina, Inna; Chaganti, Raju S. K.; Zelenetz, Andrew D.; Bachvarova, Rosemary F.; Besmer, Peter (1)
CS (1) Mol. Biol., Memorial Sloan-Kettering Inst. and Cornell Univ. Graduate Sch. Med. Sci., New York, NY 10021 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 9, pp. 3754-3758.
ISSN: 0027-8424.
DT Article
LA English
AB The receptor tyrosine kinases (RTKs) **c-kit** and platelet-derived growth factor receptor alpha chain (PDGFRa) are encoded at the white spotting (W) and patch (Ph) loci on mouse chromosome 5. While W mutations affect melanogenesis, gametogenesis, and hematopoiesis, the Ph mutation affects melanogenesis and causes early lethality in homozygotes. W-sash (W-sh) is an expression mutation and blocks **c-kit** expression in certain cell types and enhances **c-kit** expression in others, including at sites important for early melanogenesis. We have determined the effect of Ph on **c-kit** expression during embryogenesis in Ph heterozygotes. Immunohistochemical analysis revealed enhanced **c-kit** expression in several cell types, including sites important for early melanogenesis. We propose that in both W-sh and Ph mutant mice **c-kit** misexpression affects early melanogenesis and is responsible for the **pigment** deficiency. Moreover, we have defined the organization of the RTKs in the W/Ph region on chromosome 5 and characterized the Ws-sh mutation by using pulsed-field gel electrophoresis. Whereas the order of the RTK genes was determined as Pdgfra-**c-kit**-flk1, analysis of the W-sh mutation revealed that the **c-kit** and Pdgfra genes are unlinked in W-sh, presumably because of an inversion of a small segment of chromosome 5. The Ph mutation consists of a deletion including Pdgfra and the 3' deletion endpoint of Ph lies between Pdgfra and **c-kit**. Therefore, positive 5' upstream elements controlling **c-kit** expression in mast cells and some other cell types are affected by the W-sh mutation and negative elements are affected by both the W-sh and the Ph mutation.

L66 ANSWER 44 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:255111 BIOSIS
DN PREV199598269411
TI Phenotypic characterization of skin lesions in urticaria **pigmentosa** and mastocytomas.
AU Haas, Norbert (1); Hamann, Kathrin; Grabbe, Juergen; Algermissen, Bernd; Czarnetzki, Beate M.
CS (1) Dep. Dermatol., UKRV, Freie Univ., Augustenburgerplatz 1, D-13344 Berlin Germany
SO Archives of Dermatological Research, (1995) Vol. 287, No. 3-4, pp. 242-248.
ISSN: 0340-3696.
DT Article
LA English
AB In order to identify possible cellular abnormalities in human mastocytosis, sections from 13 urticaria **pigmentosa** lesions and 5 mastocytomas were compared with 5 normal skin specimens using histochemical, enzyme histochemical and immunohistochemical techniques. All toluidine blue-positive mast cells also reacted with Fc-epsilon-RI and **c-kit** antibodies, almost all stained for tryptase, many for chymase and the myeloid workshop mast cell antibodies, few for Fc-epsilon-RII and none for the proliferation marker Ki-67. Urticaria

pigmentosa lesions contained fewer epidermal Langerhans cells and a lower percentage of avidin-positive mast cells than mastocytomas and normal skin. Mastocytomas exhibited generally weaker staining for mast cell markers and mostly lacked Fc-epsilon-RI-bound IgE on mast cells and Langerhans cells, although the receptor was able to bind IgE in tissue sections. Most of the mast cell antibodies also reacted with other cell types. Only toluidine blue, avidin, tryptase and chymase stains were mast cell specific. Mast cells in mastocytosis thus differed only to a minor degree from normal mast cells, although distinct pathomechanisms may play a role in urticaria **pigmentosa** and mastocytosis.

L66 ANSWER 45 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:250178 BIOSIS
DN PREV199598264478
TI Mutations at the W locus affect survival of neural crest-derived melanocytes in the mouse.
AU Cable, Joanne (1); Jackson, Ian J.; Steel, Karen P.
CS (1) Sch. Biol. Sci., Univ. Bristol, Bristol BS8 1UG UK
SO Mechanisms of Development, (1995) Vol. 50, No. 2-3, pp. 139-150.
ISSN: 0925-4773.
DT Article
LA English
AB The development of melanoblasts in normally **pigmented** and dominant spoiling (W) embryos was followed by in situ hybridization to TRP-2/DT mRNA, which labels migratory melanoblasts from 10 days post coitum. Numerous melanoblasts migrate to the inner ear around 11 days. In contrast, few migratory melanoblasts are associated with the eye or skin at this stage and melanoblast distribution within the trunk and tail is patchy. The distribution of melanoblasts in 10.5-11-day-old W-v/W-v, W-sh/W-sh and W-41/W-41 mutants was similar to that in controls but melanoblast density was lower and by 12 days was severely reduced. These results suggest that mutations of the **c-kit** receptor tyrosine kinase encoded at the W locus do not alter early migration or differentiation of melanoblasts but severely affect melanoblast survival.

L66 ANSWER 46 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:157954 BIOSIS
DN PREV199598172254
TI The role of mast cells in the development of skin fibrosis in tight-skin mutant mice.
AU Everett, Eric T.; Pablos, Jose L.; Harley, Russell A.; Leroy, E. Carwile; Norris, James S. (1)
CS (1) Div. Rheumatol. Immunol., CSB 912, Med. Univ. S.C., 171 Ashley Ave., Charleston, SC 29425-2229 USA
SO Comparative Biochemistry and Physiology A Comparative Physiology, (1995) Vol. 110, No. 2, pp. 159-165.
ISSN: 0300-9629.
DT Article
LA English
AB Chronic **inflammatory** conditions can evolve a fibrotic phenotype often associated with an increase in the number of mast cells (MC) near or within the granulation tissue. Despite the potential of MC to mediate fibrosis, it is unclear whether these cells play a central role in the pathogenesis of fibrosis or whether their presence is simply circumstantial. The tight-skin (Tsk) mouse develops an inherited fibrotic disease (sharing many similarities with the human disease scleroderma, systemic sclerosis) in which the lesions are associated with increased numbers and heightened granule release implicating MC in the pathogenesis of fibrosis. Despite their close association with the skin fibrosis of Tsk mice, the precise role of the MC in the pathogenesis of this inherited disease is unknown. Therefore, to assess directly whether MC are key elements in the pathogenesis of Tsk fibrosis, we generated MC deficient mice carrying the Tsk locus by utilizing selective interbreeding between Tsk and mutant mice deficient in mast cells (W, dominant white-spotting). We found that in the absence of MC, the early natural history of Tsk fibrosis was not altered. Furthermore, in older (5-7 months) Tsk mice, we

found that the number of cutaneous MC was correlated with a more pronounced fibrosis. Therefore, we conclude that Tsk skin lesions are a pleiotropic manifestation of the Tsk gene in which MC are involved/ recruited by an uncharacterized mechanism and that subsequent proliferation and activation of MC leads to augmentation of fibrosis.

L66 ANSWER 47 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:157919 BIOSIS
DN PREV199598172219
TI Expression of the **c-kit** receptor in hypomelanosis: A comparative study between **piebaldism**, naevus **depigmentosus** and vitiligo.
AU Dippel, E. (1); Haas, N.; Grabbe, J.; Schadendorf, D.; Hammann, K.; Czarnetzki, B. M.
CS (1) Inst. Pharmakologie, Freie Univ. Berlin, Thielallee 67-73, C-14195 Berlin Germany
SO British Journal of Dermatology, (1995) Vol. 132, No. 2, pp. 182-189. ISSN: 0007-0963.
DT Article
LA English
AB In order to investigate possible alterations in **c-kit** protein expression on epidermal melanocytes in different **hypopigmentary** disorders, we have examined skin specimens from one patient with piebaldism, one patient with naevus **depigmentosus**, and five patients with vitiligo. Cryosections were examined by immunohistochemistry using monoclonal antibodies against the **c-kit** protein (YB5.B8) and melanosomes (TA99). In piebaldism, hypomelanotic epidermis contained only a few TA-99-positive epidermal melanocytes and no detectable **c-kit** protein, whereas in naevus **depigmentosus** the expression of **c-kit** protein was strong, and TA99 immunoreactivity was faint. In vitiligo lesions, no epidermal immunoreactivity for melanosomes or **c-kit** protein was found. Normally **pigmented** skin of all patients showed immunoreactivity of epidermal melanocytes for both **c-kit** protein and melanosomes. Different hypomelanotic lesions can thus be differentiated by absent melanocyte **c-kit** protein and low or no expression of melanosomal marker in piebaldism, normal but low melanosome expression in naevus **depigmentosus**, and the absence of all melanocyte markers in vitiligo.

L66 ANSWER 48 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:126035 BIOSIS
DN PREV199598140335
TI Melanocyte mitogens induce both melanocyte chemokinesis and chemotaxis.
AU Horikawa, Tatsuya; Norris, David A.; Yohn, Joseph J.; Zekman, Tamara; Travers, Jeffrey B.; Morelli, Joseph G. (1)
CS (1) Dep. Dermatology B-153, Univ. Colorado Sch. Med., 4200 East Ninth Ave., Denver, CO 80262 USA
SO Journal of Investigative Dermatology, (1995) Vol. 104, No. 2, pp. 256-259. ISSN: 0022-202X.
DT Article
LA English
AB It is believed that during **repigmentation** of vitiligo, inactive melanocytes in the outer root sheath of the hair follicle become activated, proliferate, and migrate into the **depigmented** skin. However, the mechanisms controlling melanocyte migration remain to be elucidated. In this study, we investigated the effects of well-described melanocyte growth factors on melanocyte migration. Using time-lapse photography, we demonstrated that melanocyte chemokinetic movement was induced by basic fibroblast growth factor, **stem cell factor**, and endothelin-1, with the greatest effect noted using 100 nM endothelin-1. Similar results were reported previously with leukotriene C-4. When surrounded by these stimuli, melanocytes moved in a random, nonlinear fashion and showed no desensitization at the concentrations studied. In Boyden chamber checkerboard analysis, basic fibroblast growth

factor, leukotriene C-4 and endothelin-1 were chemotactic. They produced directional migration and showed desensitization at higher concentrations. The greatest effect again was seen with 100 nM endothelin-1. **Stem cell factor** showed no effect in this assay system at the concentrations tested. The four melanocyte mitogens-leukotriene C-4, endothelin-1, basic fibroblast growth factor, and **stem cell factor**-stimulate melanocyte migration, and this migration may be either chemokinetic (activated random movement) or chemotactic (requiring a gradient, directional, and showing desensitization), depending on the conditions used. We believe that these factors may be effective in stimulating vitiligo **repigmentation** by inducing proliferation and migration of hair-follicle outer-root-sheath melanocytes into the **depigmented** epidermis.

L66 ANSWER 49 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:108942 BIOSIS
DN PREV199598123242
TI Human dermal endothelial cells express membrane-associated mast cell growth factor.
AU Weiss, Rochelle R.; Whitaker-Menezes, Diana; Longley, Jack; Bender, Jeff; Murphy, George F. (1)
CS (1) Duhring Res. Lab., Dep. Dermatology, Univ. Pa., 235B CRB, 422 Curie Boulevard, Philadephia, PA 19104 USA
SO Journal of Investigative Dermatology, (1995) Vol. 104, No. 1, pp. 101-106. ISSN: 0022-202X.
DT Article
LA English
AB Mast cell growth factor (MGF), a molecule that serves as a ligand for the receptor tyrosine kinase **c-kit**, is important in mast cell differentiation, migration, and activation. Previous studies of paraffin-embedded human skin using antibody to murine MGF and reverse transcription-polymerase chain reaction have demonstrated MGF protein and mRNA expression in keratinocytes and isolated dermal cells. We utilized a monoclonal antibody to human MGF to further define patterns of immunoreactivity in frozen specimens of neonatal and adult skin from normal individuals and from patients with urticaria **pigmentosa**. In addition to keratinocytes and isolated dermal cells in normal and urticaria **pigmentosa** skin, MGF was detected in cells lining superficial and mid-dermal vessels. Co-expression of MGF and the vascular antigen CD31, and immunoelectron microscopy, identified MGF-positive cells as endothelial cells. Patterns of endothelial MGF expression were not influenced by mast cell degranulation and endothelial E-selectin induction in vitro. By ultrastructure, unfixed specimens demonstrated MGF expression both within the endothelial cytoplasm and in association with lumenal, but not ablumenal, surfaces. Specimens fixed with Nakane's solution had diminished endothelial cytoplasmic MGF reactivity, but lumenal expression was maintained, suggesting persistence of a membrane-associated reactivity. MGF mRNA was also detected in cultured dermal microvascular endothelial cells using reverse transcription-polymerase chain reaction. These data establish human dermal endothelial cells as sites of MGF production and expression in human skin. Mast cell precursors must home to skin via vascular channels and differentiate in the immediate perivascular space. Thus, endothelial MGF may be an important determinant of adhesion and differentiation of mast cell progenitors expressing receptors for MGF.

L66 ANSWER 50 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:34599 BIOSIS
DN PREV199598048899
TI Molecular basis of human **piebaldism**.
AU Spritz, Richard A.
CS Dep. Med. Genetics Pediatrics, 317 Laboratory Genetics, 445 Henry Mall, Univ. Wisconsin, Madison, WI 53706 USA
SO Journal of Investigative Dermatology, (1994) Vol. 103, No. 5 SUPPL., pp. 137S-140S.
ISSN: 0022-202X.
DT Article

LA English
AB Piebaldism is an autosomal dominant genetic disorder of **pigmentation** characterized by congenital patches of white skin and hair that lack melanocytes. Piebaldism results from mutations of the **KIT proto-oncogene**, which encodes the cell-surface receptor transmembrane tyrosine kinase for an embryonic growth factor, Steel factor. Several pathologic mutations of the **KIT** gene have now been identified in different patients with piebaldism. Correlation of these mutations with the associated piebald phenotypes has led to the recognition of a hierarchy of three classes of mutations that result in a graded series of piebald phenotypes, and to improved understanding of the mechanisms that underlie dominant genetic disorders.

L66 ANSWER 51 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:526701 BIOSIS
DN PREV199497539701
TI Comparative cytokine release from human monocytes, monocyte-derived immature mast cells, and a human mast cell line (HMC-1.
AU Grabbe, Juergen (1); Welker, Pia; Moeller, Annelie; Dippel, Edgar; Ashman, Leonie K.; Czarnetzki, Beate M.
CS (1) Freie Univ. Berlin, Rudolf-Virchow Clin., Dep. Dermatol., Augustenburgerplatz 1, D 13344 Berlin Germany
SO Journal of Investigative Dermatology, (1994) Vol. 103, No. 4, pp. 504-508. ISSN: 0022-202X.
DT Article
LA English
AB To obtain further information regarding the role of cytokines during mast cell differentiation, we have investigated changes of cytokine secretion in mast cells developing from the human peripheral blood monocytic cell fraction during culture with fibroblast-derived condition media. The influence of **stem cell factor** and an antibody to the respective receptor in our culture system was studied as well. interleukin (IL)-1-alpha, 1-beta, IL-6, and tumor necrosis factor (TNF)alpha were spontaneously secreted by cultured cells at day 1 and decreased markedly by day 14. Similar changes occurred also during culture with **stem cell factor** and were partially abrogated by an anti-receptor antibody. IL-8 was secreted at a high level throughout the culture, whereas no spontaneous secretion of IL-2, IL-3, IL-4, and IL-7 was measured at all. Upon stimulation with phorbol myristate acetate and A23187, cultured cells showed substantially more release of IL-3 and TNF-alpha after 14 d of culture, compared to peripheral blood monocytic cells. Preformed TNF-alpha was found in one of three monocytic cell preparations from peripheral blood, but not in monocytic cell-derived mast cells. During mast cell differentiation, cytokines from monocytic cells are therefore downregulated while the cells assume a pattern typically found in mast cells.

L66 ANSWER 52 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:406324 BIOSIS
DN PREV199497419324
TI Inhibition of proliferation of human melanocytes by a KIT antisense oligodeoxynucleotide: Implications for human **piebaldism** and mouse dominant white spotting (W.
AU Spritz, Richard A. (1); Ho, Lingling; Strunk, Kathleen M.
CS (1) 317 Laboratory Genetics, 445 Henry Mall, Univ. Wis., Madison, WI 53706 USA
SO Journal of Investigative Dermatology, (1994) Vol. 103, No. 2, pp. 148-150. ISSN: 0022-202X.
DT Article
LA English
AB KIT constitutes the cell surface transmembrane receptor protein tyrosine kinase for a growth factor variously termed steel factor (SLF), **stem cell factor**, mast cell growth factor, or Kit ligand. Inherited mutations of the KIT gene result in piebaldism in humans and dominant white spotting (W) in mice. Patches of

hypopigmented skin and hair in these disorders represent regions lacking in melanocytes, the result of defective melanoblast differentiation, migration, proliferation, or survival during embryonic development. Here we show that incubation of normal human melanocytes with a KIT antisense oligodeoxynucleotide greatly inhibits cell proliferation in culture, whereas incubation with a KIT sense oligodeoxy-nucleotide has no effect. The KIT oligodeoxynucleotides also had little or no effect on cell survival.

L66 ANSWER 53 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:343526 BIOSIS
DN PREV199497356526
TI The kit-**ligand** (steel factor) and its receptor **c-kit**/W: Pleiotropic roles in gametogenesis and melanogenesis.
AU Besmer, Peter (1); Manova, Katia; Duttlinger, Regina; Huang, Eric J.; Packer, Alan; Gyssler, Corina; Bachvarova, Rosemary F.
CS (1) Mol. Biol. Prog. Sloan-Kettering Inst., Cornell Univ. Graduate Sch. Med. Sci., New York, NY 10021 USA
SO Development (Cambridge), (1993) Vol. 0, No. SUPPL., pp. 125-137. ISSN: 0950-1991.
DT Article
LA English
AB The **c-kit** receptor tyrosine kinase belongs to the PDGF/CSF-1/**c-kit** receptor subfamily. The kit-ligand, KL, also called steel factor, is synthesized from two alternatively spliced mRNAs as transmembrane proteins that can either be proteolytically cleaved to produce soluble forms of KL or can function as cell-associated molecules. The **c-kit** receptor kinase and KL are encoded at the white spotting (W) and steel (Sl) loci of the mouse, respectively. Mutations at both the W and the Sl locus cause deficiencies in gametogenesis, melanogenesis and hematopoiesis. The **c-kit** receptor is expressed in the cellular targets of W and Sl mutations, while KL is expressed in their microenvironment. In melanogenesis, **c-kit** is expressed in melanoblasts from the time they leave the neural crest and expression continues during embryonic development and in the melanocytes of postnatal animals. In gametogenesis **c-kit** is expressed in primordial germ cells, in spermatogonia, and in primordial and growing oocytes, implying a role at three distinct stages of gametogenesis. Many mutant alleles are known at W and Sl loci and their phenotypes vary in the degree of severity in the different cellular targets of the mutations. While many W and Sl alleles severely affect primordial germ cells (PGC), several mild Sl alleles have weak effects on PGCs and exhibit differential male or female sterility. Steel Panda (Sl-pan) is a KL expression mutation in which KL RNA transcript levels are reduced in most tissues analyzed. In female Sl-pan/Sl-pan mice, ovarian follicle development is arrested at the one layered cuboidal stage as a result of reduced KL expression in follicle cells, indicating a role for **c-kit** in oocyte growth. W-sh is a **c-kit** expression mutation, which affects mast cells and melanogenesis. While the mast cell defect results from lack of **c-kit** expression, the **pigmentation** deficiency appears to stem from ectopic **c-kit** receptor expression in the somitic dermatome at the time of migration of melanoblasts from the neural crest to the periphery. It is proposed that the ectopic **c-kit** expression in W-sh mice affects early melanogenesis in a dominant fashion. The sash" or white belt of W-sh/+ animals and some other mutant mice is explained by the varying density of melanoblasts along the body axis of wild-type embryos.

L66 ANSWER 54 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:272085 BIOSIS
DN PREV199497285085
TI **Stem cell factor** regulates human melanocyte-matrix interactions.
AU Scott, Glynis (1); Ewing, James; Ryan, Daniel; Abboud, Camille
CS (1) Box 697, Dep. Dermatol., Univ. Rochester Sch. Med., Rochester, NY

14642 USA
SO Pigment Cell Research, (1994) Vol. 7, No. 1, pp. 44-51.
ISSN: 0893-5785.
DT Article
LA English
AB **Stem cell factor** (SCF) is hypothesized to play a critical role in the migration of melanocytes during embryogenesis because mutations in either the SCF gene, or its ligand, **c-kit**, result in defects in coat **pigmentation** in mice and in skin **pigmentation** in humans. In this report we directly show that SCF alters the adhesion and migration of human melanocytes to extracellular matrix (ECM) ligands and regulates integrin expression at the protein level. SCF decreased adhesion of neonatal and fetal cells to collagen IV; and increased attachment of fetal cells to laminin. Attachment of fetal cells to fibronectin was decreased, but was unchanged in neonatal cells. Flow cytometry analysis of neonatal melanocytes showed that SCF down-regulated the expression of the alpha-2 receptor, and up-regulated the expression of the alpha-3, alpha-5 and beta-1 integrin receptors. SCF down-regulated expression of alpha-2, alpha-5 and beta-1 integrins by fetal melanocytes, and up-regulated expression of the alpha-v and alpha-3 integrin receptors. Analysis of melanocyte migration using time-lapse videomicroscopy showed that SCF significantly increased migration of neonatal, but not fetal, melanocytes on fibronectin (FN). We conclude that SCF regulates integrin expression at the protein level and that SCF has pleiotropic effects on melanocyte attachment and migration on ECM ligands. We suggest that this may be one mechanism by which SCF regulates melanocyte migration during development of the skin.

L66 ANSWER 55 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:270581 BIOSIS
DN PREV199497283581
TI Effects of mutations at the W locus (**c-kit**) on inner ear **pigmentation** and function in the mouse.
AU Cable, J. (1); Huszar, D.; Jaenisch, R.; Steel, K. P.
CS (1) Sch. Biological Sci., Univ. Bristol, Woodland Road, Bristol BS8 1UG UK
SO Pigment Cell Research, (1994) Vol. 7, No. 1, pp. 17-32.
ISSN: 0893-5785.
DT Article
LA English
AB The W locus encodes a tyrosine kinase receptor, **c-kit**, which affects survival of melanoblasts from the neural crest. The primary cochlear defect in Viable Dominant Spotting (W-v/W-v) mutants is a lack of melanocytes within the stria vascularis (SV) associated with an endocochlear potential (EP) close to zero and hearing impairment. In this study, we compare inner ear **pigmentation** with cochlear potentials in three other W alleles (W-x, W-sh, and W-41) and reveal an unequivocal correlation between presence of strial melanocytes and presence of an EP. Asymmetry was common, and 8.3% of W-sh/W-x, 25% of W-sh/W-sh, 60% of W-41/W-x, and 69.2% of W-41/W-41 ears had a **pigmented** stria and an EP, while the remainder had no strial melanocytes and no EP. In those mutants that partially escaped the effects of the mutation, strial melanocytes rarely extended the entire length of the stria, but were confined to the middle and/or basal turns of the cochlea. The extent of strial **pigmentation** was unrelated to the EP value, which was measured from the basal turn only. Compound action potential (CAP) responses recorded from ears with an EP were variable and they showed greatly raised thresholds or were absent in all ears where the EP was close to zero. In controls, melanocytes in the vestibular part of the ear were found in the utricle, crus commune, and ampullae, whereas in many mutants only one or two of these regions were **pigmented**. There was a broad correlation between **pigmentation** of the stria and **pigmentation** of the vestibular region but this was not absolute. All W-41/W-x, W-sh/W-sh, and W-41/W-41 mutants had some **pigment** on the pinna but, in contrast to controls where melanocytes were found in the epidermis and dermis of the pinna, **pigment** cells were reduced in number and generally restricted to

the dermis. Injection of normal neural crest cells into 9.5-day-old mutant embryos increased the extent of skin **pigmentation** on the head and coat of adult chimeras and was associated with a small increase in the proportion of **pigmented** strias.

L66 ANSWER 56 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:178214 BIOSIS
DN PREV199497191214
TI The molecular genetics of albinism and **piebaldism**.
AU Tomita, Yasushi (1)
CS (1) Dep. Dermatology, Akita University School Medicine, Akita 010 Japan
SO Archives of Dermatology, (1994) Vol. 130, No. 3, pp. 355-358.
ISSN: 0003-987X.
DT General Review
LA English
AB Background: Oculocutaneous albinism (OCA) is an autosomal-recessive genetic disorder defined by hypomelanosis in the eyes, hair, and skin. Piebaldism is an autosomal-dominant congenital leukoderma associated with a white forelock. The molecular pathogeneses of these congenital **pigmentary** disorders have been clarified in recent years and are briefly reviewed here. Observations: The pathologic gene mutations causing OCA and piebaldism are as follows. When a mutated tyrosinase gene produces inactive, less active, or temperature-sensitive tyrosinase, its phenotype is tyrosinase-negative (type I-A), yellow-mutant (type I-B), or temperature-sensitive (type I-TS) OCA, respectively. Mutation of the P gene encoding the tyrosine-transporting membrane protein probably occurs in tyrosinase-positive OCA (type II). A heterozygous mutation of the **c-kit** gene encoding mast cell-stem cell growth factor receptor induces piebaldism. Conclusion: The molecular bases of several types of OCA and piebaldism have been elucidated by gene technology, and other gene mutations causing OCA or many other **pigmentary** disorders will be clarified in the near future.

L66 ANSWER 57 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:432736 BIOSIS
DN PREV199396087361
TI Novel mutations of the **KIT** (Mast/stem cell growth factor receptor) **proto-oncogene** in human **piebaldism**
.
AU Spritz, Richard A. (1); Holmes, Stuart A.; Itin, Peter; Kuester, Wolfgang
CS (1) 317 Lab. Genetics, 445 Henry Mall, Univ. Wisconsin, Madison, WI 53706 USA
SO Journal of Investigative Dermatology, (1993) Vol. 101, No. 1, pp. 22-25.
ISSN: 0022-202X.
DT Article
LA English
AB Piebaldism is an autosomal dominant genetic disorder of **pigmentation** characterized by congenital patches of white skin and hair that lack melanocytes. Piebaldism results from mutations of the **KIT proto-oncogene**, which encodes the cellular receptor transmembrane tyrosine kinase for mast/stem cell growth factor. Here we describe two novel **KIT** mutations associated with human piebaldism. These amino acid substitutions, located in the most highly conserved sections, of the **KIT** kinase domain, would be expected to dominant-negatively inhibit **KIT**-dependent signal transduction, resulting in aberrant melanocyte proliferation or migration during embryologic development.

L66 ANSWER 58 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:430490 BIOSIS
DN PREV199396085115
TI W-sash affects positive and negative elements controlling **c-kit** expression: Ectopic **c-kit** expression at sites of kit-**ligand** expression affects melanogenesis.
AU Duttlinger, Regina; Manova, Katia; Chu, Tang Y.; Gyssler, Corina; Zelenetz, Andrew D.; Bachvarova, Rosemary F.; Besmer, Peter (1)

CS (1) Molecular Biol. Program, Sloan-Kettering Inst., 1275 York Ave., New York, NY 10021 USA
SO Development (Cambridge), (1993) Vol. 118, No. 3, pp. 705-717. ISSN: 0950-1991.
DT Article
LA English
AB The receptor tyrosine kinase **c-kit** and its cognate ligand KL are encoded at the white spotting (W) and steel (Sl) loci of the mouse, respectively. Mutations at both the W and the Sl locus cause deficiencies in gametogenesis, melanogenesis and hematopoiesis (erythrocytes and mast cells). The W-sash mutation differs from most W mutations in that it affects primarily mast cells and melanogenesis but not other cellular targets of W and Sl mutations. Thus, W-sh/W-sh mice are fertile and not anemic, but they lack mast cells in their skin and intestine and are devoid of coat **pigment**. Heterozygotes are black with a broad white sash/belt in the lumbar region. In order to determine the basis for the phenotypes of W-sash mice, we investigated **c-kit** RNA and protein expression patterns in adult W-sh/W-sh mice and during embryonic development. We show that **c-kit** expression is absent in bone-marrow-derived W-sh/W-sh mast ells, the fetal and the adult lung, and the digestive tract at embryonic day 13 1/2 (E13 1/2), tissues that normally express **c-kit**. Unexpectedly, in E10 1/2 and 11 1/2 d W-sh/W-sh embryos, we found **c-kit** expression in the dermatome of the somites, the mesenchyme around the otic vesicle and the floorplate of the neural tube, structures known to express the **c-kit** ligand in wild-type embryos. The ectopic **c-kit** expression in W-sh homozygous embryos does not affect **c-kit** ligand expression. The presumed W-sh/W-sh melanoblasts appeared to be normal and, at E10 1/2, similar numbers were found in normal and homozygous mutant embryos. At E13 1/2 +/+ embryos had a graded distribution of melanoblasts from cranial to caudal with a minimum in the lumbar region. Whereas E13 1/2 homozygous W-sh/W-sh embryos essentially lacked **c-kit**-positive cells in the skin, E13 1/2 heterozygous W-sh/+ embryos had reduced numbers of melanoblasts compared to +/+ with few or none in the lumbar region (future sash). It is proposed that ectopic **c-kit** expression in the somitic dermatome affects early melanogenesis in a dominant fashion. Molecular analysis of W-sh chromosomal DNA revealed a deletion or rearrangement in the vicinity of the **c-kit** gene. These results provide an explanation for the W-sh phenotype and have implications for the control of **c-kit** expression.

L66 ANSWER 59 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:412187 BIOSIS
DN PREV199396077912
TI KIT **ligand** (mast cell growth factor) inhibits the growth of KIT-expressing melanoma cells.
AU Zakut, Rina (1); Perlis, Roy; Eliyahu, Siona; Yarden, Yosef; Givol, David; Lyman, Steward D.; Halaban, Ruth
CS (1) Dep. Chemical Immunology, Weizmann Inst. Science, Rehovot 76100 Israel
SO Oncogene, (1993) Vol. 8, No. 8, pp. 2221-2229. ISSN: 0950-9232.
DT Article
LA English
AB Previous studies in vivo and in vitro show that **KIT** kinase promotes normal melanocyte development and growth. However, the role of the **KIT proto-oncogene** in neoplastic melanocytes is not certain. We therefore examined **KIT** expression and function in human melanomas. Our results show that **KIT** mRNA was expressed in 12 of 28 melanoma cell lines (apprx 40%), mainly in those originating from **pigmented** tumors. Surprisingly, activation of **KIT** with mast cell growth factor (MGF) in melanoma cells produced biological responses opposite to those elicited in normal melanocytes. MGF inhibited rather than stimulated the growth of metastatic melanoma cell lines. The opposite effects may be due to aberrant signal

transduction by **KIT** in melanoma cells in response to MGF. The in vitro inhibition of melanoma cells by MGF suggests that growth in vivo of this tumor is not promoted by **KIT** kinase activation, but rather that transformed melanocytes might regress when MGF is expressed in their immediate environment.

L66 ANSWER 60 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:410496 BIOSIS
DN PREV199396076221
TI The role of **c-kit proto-oncogene** during melanocyte development in mouse: In vivo approach by the in utero microinjection of anti-**c-kit** antibody.
AU Yoshida, Hisahiro; Nishikawa, Shin-Ichi; Okamura, Hitoshi; Sakakura, Teruyo; Kusakabe, Moriaki (1)
CS (1) Lab. Cell Biology, Tsukuba Life Science Cent., Inst. Physical Chemical Res., Koyadai, Tsukuba, Ibaraki 305 Japan
SO Development Growth & Differentiation, (1993) Vol. 35, No. 2, pp. 209-220. ISSN: 0012-1592.
DT Article
LA English
AB In order to investigate the role of the **c-kit** oncogene in the melanoblast development, a rat monoclonal antibody (ACK2) against the mouse **c-kit** protein was used to localize cells expressing **c-kit** during fetal development. ACK2 was also injected directly into the amniotic cavity of mouse fetuses at successive developmental stages. After birth, the offspring were examined to determine the resulting coat color patterns. **c-kit** positive melanoblasts first appeared in dermis of fetuses at 11.5 days postcoitum (dpc). Subsequently, these cells increased in number and migrated dorsolaterally to the ventral region, and by 12.5 dpc some of them began to invade the epidermis. Treatment of fetuses by ACK2 microinjection appeared to affect the **pigmentation** in the coat, inducing a variety of spotting patterns in offspring, and the location of the spots was closely correlated with gestational stage. ACK2 injection of early fetuses produced major changes in coat color even though few **c-kit** positive cells were detectable in the dermal mesenchyme at the time of injection. Large spots were also induced when mid-stage fetuses with a only few **c-kit** positive cells in the dorsal region were injected. By contrast, except for spot formation in the center of ventral region, ACK2 injection did not appear to affect melanogenesis in late stage fetuses that had many **c-kit** positive cells.

L66 ANSWER 61 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:366427 BIOSIS
DN PREV199396052102
TI Altered metabolism of mast-cell growth factor (**c-kit ligand**) in cutaneous mastocytosis.
AU Longley, B. Jack, Jr. (1); Morganroth, Greg S.; Tyrrell, Lynda; Ding, Tie Gang; Anderson, Dirk M.; Williams, Douglas E.; Halaban, Ruth
CS (1) Yale Univ. Sch. Med., Dep. Dermatol., 333 Cedar St., P.O. Box 3333, LCI 500, New Haven, CT 06510 USA
SO New England Journal of Medicine, (1993) Vol. 328, No. 18, pp. 1302-1307. ISSN: 0028-4793.
DT Article
LA English
AB Background and Methods: The lesions of cutaneous mastocytosis are characterized by dermal infiltrates of mast cells and may appear **hyperpigmented** because of the presence of increased levels of epidermal melanin. Mast-cell growth factor, the ligand for the product of the **c-kit proto-oncogene**, stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. We therefore looked for the expression of the mast-cell growth factor gene in the skin of patients with cutaneous mastocytosis using immunohistochemical techniques and the polymerase chain reaction. Results: In the skin of normal subjects and those with unrelated

diseases, immunoreactive mast-cell growth factor was associated with keratinocytes and scattered dermal cells, a pattern consistent with cell-bound mast-cell growth factor. In skin samples containing lesions and in clinically normal skin from patients with mastocytosis, however, mast-cell growth factor was also found free in the dermis and in the extracellular spaces between keratinocytes, suggesting the presence of a soluble form of this protein. Messenger RNA (mRNA) that can encode soluble mast-cell growth factor was present in the skin of patients as well as in that of normal control subjects. No sequence abnormalities were detected in mRNA for mast-cell growth factor from one patient. Conclusions: The altered distribution of mast-cell growth factor in the skin of patients with cutaneous mastocytosis is consistent with abnormal production of the soluble form of this factor. This abnormality is probably due to increased proteolytic processing, since it was not explained by differences in the splicing or sequence of mast-cell growth factor mRNA in the patients. Soluble mast-cell growth factor may cause the characteristic accumulation of mast cells and the **hyperpigmentation** of skin found in cutaneous mastocytosis. These findings suggest that some forms of mastocytosis represent reactive hyperplasia rather than mast-cell neoplasia.

L66 ANSWER 62 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:342701 BIOSIS
DN PREV199396039701
TI Mast cell number in the skin of heterozygotes reflects the molecular nature of **c-kit** mutation.
AU Tsujimura, Tohru; Koshimizu, Uichi; Katoh, Hideki; Isozaki, Koji; Kanakura, Yuzuru; Tono, Toshiharu; Adachi, Shiro; Kasugai, Tsutomu; Tei, Hideki; et al.
CS Dep. Pathology, Osaka Univ. Med. Sch., Yamada-oka 2-2, Suita 565 Japan
SO Blood, (1993) Vol. 81, No. 10, pp. 2530-2538.
ISSN: 0006-4971.
DT Article
LA English
AB The W locus of mice encodes the **c-kit** receptor tyrosine kinase. Heterozygous W-Jic/+ and W-n/+ mice and homozygous W-f/W-f mice were similar in appearance; all of them have large **depigmented** areas lacking any well-defined pattern. The W-Jic, W-n, and W-f mutant alleles were characterized and their molecular nature was correlated with the mast cell differentiation in the skin and the biologic features of cultured mast cell (CMC). All W-Jic, W-n, and W were point mutations at the tyrosine kinase domain, and **c-kit** mRNA was normally transcribed from all of them. The mature 145-Kd form of the **c-kit** protein was produced from the W-Jic and W-f alleles, but not from the W-n allele. **c-kit** proteins produced by the W-Jic or W-f allele were expressed on the surface of CMCs, but those of the W-n allele were not. When double heterozygous mice were produced between Wand W-Jic and between W and W-n, both W/W-Jic and W/W-n mice lacked skin mast cells. W/W-Jic CMCs and W/W-n CMCs did not survive in the coculture with fibroblasts. W/W-Jic CMCs normally attached to fibroblasts, but W/W-n CMCs did not. The defect of W/W-n CMCs in the attachment was attributed to the deficient extracellular expression of the **c-kit** protein. The number of skin mast cells was compared among W-Jic/+, W-n/+, W-f/+, and W-f/W-f mice. Mast cells decreased in W-Jic/+ and W-f/W-f mice, but not in W-n/+ and W-f/+ mice. Although the W-n was a point mutation at the kinase domain, the biologic effect of the W-n was comparable with that of the W mutant allele, which produces truncated **c-kit** protein without the transmembrane domain. The weak phenotype of W-n/+ mice may be explained by the deficient extracellular expression of **c-kit** proteins produced by the W-n allele. When W-Jic/, W-n/W-n, and W-f/W-f CMCs were stimulated by the recombinant **c-kit** ligand, autophosphorylation activity was observed only in W-f/W-f CMCs. This result was consistent with the weak biologic effect of the W-f mutant allele.

L66 ANSWER 63 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:215211 BIOSIS
DN PREV199344099711
TI Steel factor and **c-kit** receptor: From mutants to a growth factor system.
AU Morrison-Graham, Kathleen; Takahashi, Yoshiko
CS Inst. Neuroscience, Univ. Oregon, Eugene, Orgeon 97403 USA
SO Bioessays, (1993) Vol. 15, No. 2, pp. 77-83.
ISSN: 0265-9247.
DT General Review
LA English

L66 ANSWER 64 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:170573 BIOSIS
DN PREV199395091623
TI Characteristics of stria vascularis melanocytes of viable dominant spotting (W-v/W-v) mouse mutants.
AU Cable, J. (1); Barkway, C.; Steel, K. P.
CS (1) MRC Inst. Hearing Res., University Park, Nottingham NG7 2RD UK
SO Hearing Research, (1992) Vol. 64, No. 1, pp. 6-20.
ISSN: 0378-5955.
DT Article
LA English
AB The W-V mutation lies in the kinase domain of the **proto-oncogene c-kit** which is expressed in a variety of cells including neural crest derived melanoblasts. The mutation results in the abnormal migration proliferation, survival and/or differentiation of melanoblasts. Viable Dominant Spotting (W-v/W-v) mouse mutants have a white coat due to the absence of melanocytes. The majority of these animals have no melanocytes within the stria vascularis and no endocochlear potential (EP). A proportion of homozygous mutants partially escape the effects of the mutation: 47.2% of pinnae and 21% of vestibular regions were **pigmented** and 10.8% of ears had an EP. All ears with an EP that were available for histology had some **pigmentation** of the stria. There was no obvious correlation between external and internal spotting in W-v/W-v mice, and asymmetrical **pigmentation** of the ears was common. Both light and dark intermediate cells (which are derived from melanocytes) were present in the middle and/or basal turns of these cochlear ducts and they appeared to function normally in enabling the stria to produce an EP (although the EP was usually lower than normal). This suggests that the **c-kit** gene product is needed only during development of the stria, and not for mature melanocyte function because the melanocytes present in the mutant strias were carrying the mutant version of the **c-kit** gene.
Melanocytes were similar in appearance in controls and mutants, except that fewer melanin granules were observed in the strias of W-v/W-v mice. The observations that strial melanocytes with very few melanin granules in W-v/W-v mutants are able to support EP production, together with previous observations that albino animals with strial melanocytes but no melanin have a normal EP, suggest that melanocytes but not melanin are essential for normal strial function.

L66 ANSWER 65 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:50959 BIOSIS
DN PREV199395027261
TI Developmental abnormalities in Steel-17H mice result from a splicing defect in the steel factor cytoplasmic tail.
AU Brannan, C. I.; Bedell, M. A.; Resnick, J. L.; Eppig, J. J.; Handel, M. A.; Williams, D. E.; Lyman, S. D.; Donovan, P. J.; Jenkins, N. A.; Copeland, N. G. (1)
CS (1) Mammalian Genetics Lab., ABL-Basic Res. Program, Natl. Cancer Inst.-Frederick Cancer Res. and Dev. Cent., Frederick, Md. 21702
SO Genes & Development, (1992) Vol. 6, No. 10, pp. 1832-1842.
ISSN: 0890-9369.
DT Article
LA English

AB The murine dominant White spotting (W) and Steel (Sl) loci encode the **c-kit** tyrosine kinase receptor and its cognate ligand steel factor (SLF), respectively. Mutations at either locus produce deficiencies in the same three migratory cell populations-those giving rise to **pigment** cells, germ cells, and blood cells. The identification of the gene products of these two loci combined with the plethora of W and Sl mutations available for molecular analysis offers a unique opportunity to dissect the role of a tyrosine kinase receptor and its cognate ligand during development in a fashion not possible for most other mammalian genes. Among the most interesting Sl mutations available for study are those that induce sterility in only one sex. In studies described here, we show that one of these alleles, Sl-17H, which in the homozygous condition induces sterility in males but not females, is the result of a splicing defect in the SLF cytoplasmic tail. We also characterize the nature of the germ cell defects in male and female Sl-1-7-H mice and show that both sexes are affected equally during embryonic but not postnatal development. These studies provide new insights into the role of SLF in germ cell development and indicate that the cytoplasmic domain of SLF is important for its normal biological function.

L66 ANSWER 66 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:428523 BIOSIS
DN BA94:80648
TI THE HUMAN RECOMBINANT **C-KIT** RECEPTOR LIGAND RHSCF INDUCES MEDIATOR RELEASE FROM HUMAN CUTANEOUS MAST CELLS AND ENHANCES IGE-DEPENDENT MEDIATOR RELEASE FROM BOTH SKIN MAST CELLS AND PERIPHERAL BLOOD BASOPHILS.
AU COLUMBO M; HOROWITZ E M; BOTANA L M; MACGLASHAN D W JR; BOCHNER B S; GILLIS S; ZSEBO K M; GALLI S J; LICHTENSTEIN L M
CS DIV. ALLERGY CLIN. IMMUNOL., JOHNS HOPKINS UNIV. SCH. MED., JOHNS HOPKINS ASTHMA ALLERGY CENT., 301 BAYVIEW BLVD., BALTIMORE, MD. 21224, USA.
SO J IMMUNOL, (1992) 149 (2), 599-608.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB The gene product of the steel locus of the mouse represents a growth factor for murine mast cells and a ligand for the **c-kit** **proto-oncogene** receptor, a member of the tyrosine kinase receptor class of oncogenes (for review, see O. N. Witte. 1990. Cell 63: 5). We have studied the effect of the human recombinant **c-kit** receptor ligand **stem cell factor** (rhSCF) on the release of **inflammatory** mediators from human skin mast cells and peripheral blood basophils and compared its activity to that of rhIL-3. rhSCF (1 ng/ml to 1 .mu.g/ml) activated the release of histamine and PGD2 from mast cells isolated from human skin. Analysis by digital video microscopy indicated that purified human skin mast cells (84 .+-. 5% pure) responded to rhSCF (0.1 to .mu.g/ml) challenge with a rapid, sustained rise in intracellular Ca2+ levels that was accompanied by secretion of histamine. A brief preincubation (10 min) of mass cells with rhSCF (0.1 pg/ml to 1 ng/ml) significnatly enhanced (100 .+-. 35%) the release of histamine induced by anti-IgE (3 .mu.g/ml), but was much less effective on IgE-mediated release of PGD2. In contrast, a short term incubation with rhSCF did not potentiate the secretion of histamine activated by substance P (5 .mu.M). A 24-h incubation of mast cells with rhSCF did not affect the release of mediators induced by anti-IgE (3 .mu.g/ml), probably due to receptor desensitization. rhSCF (1 ng/ml to 3 .mu.g/ml) neither caused release of histamine or leukotriene C4 (LTC4) release from leukocytes of 14 donors, nor induced a rise in intracellular Ca2+ levels in purified (> 70%) basophils. Brief preincubation (10 min) of leukocytes with rhSCF (1 ng/ml to 3 .mu.g/ml) caused an enhancement (69 .+-. 11%) of anti-IgE-induced release of histamine that was significant at concentrations as low as 3 ng/ml ($p < 0.05$), whereas it appeared less effective in potentiating IgE-mediated LTC4 release. In contrast, a prolonged incubation (24 h) with rhSCF (0.1 pg/ml to 100 ng/ml) did not enhance the release of histamine or LTC4 induced by anti-IgE (0.1

.mu.g/ml), whereas rhIL-3 (3 ng/ml) significantly potentiated the release of both mediators. A pretreatment with a mAb directed against the human **c-kit** receptor (8 .mu.g/ml) abolished the enhancement of IgE-mediated histamine release induced by a 10-min incubation with rhSCF (1 to 3 .mu.g/ml). Indirect immunofluorescence and flow-cytometric analysis revealed that human basophils do express the **c-kit** receptor on their cell membrane, although the level of expression was much lower than that of mast cells. Our data demonstrate that rhSCF can enhance the immunologically stimulated release of histamine from human skin mast cells and peripheral blood basophils, and that the skin mast cell can be activated by this gene product. It can be hypothesized that, under certain circumstances, rhSCF may represent a mast cell or basophil activating/modulating factor in human allergic reactions. Moreover, some of the effects of rhSCF on mast cell mediator release in vitro occurred at concentrations of the cytokine similar to those present in the serum of normal subjects in vivo. This suggests that SCF may also modulate mast cell function under physiologic conditions.

L66 ANSWER 67 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:390626 BIOSIS
DN BA94:62801
TI HUMAN PIEBALD TRAIT RESULTING FROM A DOMINANT NEGATIVE MUTANT ALLELE OF THE **C-KIT** MEMBRANE RECEPTOR GENE.
AU FLEISCHMAN R A
CS SIMMONS CANCER CENTER, DEP. MED., 5323 HARRY HINES BOULEVARD, DALLAS, TEXAS 75235-8852.
SO J CLIN INVEST, (1992) 89 (6), 1713-1717.
CODEN: JCINAO. ISSN: 0021-9738.
FS BA; OLD
LA English
AB Human piebald trait is an autosomal dominant defect in melanocyte development characterized by patches of **hypopigmented** skin and hair. Although the molecular basis of piebaldism has been unclear, a phenotypically similar "dominant spotting" of mice is caused by mutations in the murine **c-kit** protoonocogene. In this regard, one piebald use with a point mutation and another with a deletion of **c-kit** have been reported, although a polymorphism or the involvement of a closely linked gene could not be excluded. To confirm the hypothesis that piebaldism results from mutations in the human gene, **c-kit** exons were amplified by polymerase chain reaction from the DNA of 10 affected subjects and screened for nucleotide changes by single-stranded conformation polymorphism analysis. In one subject with a variant single-stranded conformation polymorphism pattern for the first exon encoding the kinase domain, DNA sequencing demonstrated a missense mutation (Glu583 .fwdarw. Lys). This mutation is identical to the mouse W37 mutation which abolishes autophosphorylation of the protein product and causes more extensive **depigmentation** that "null" mutations. In accord with this "dominant negative" effect, the identical mutation in this human kindred is associated with unusually extensive **depigmentation**. Thus, the finding of a piebald subject with a mutation that impairs receptors activity strongly implicates the **c-kit** gene in the molecular pathogenesis of this human development defect.

L66 ANSWER 68 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:95921 BIOSIS
DN BA93:52471
TI ECTOPIC EXPRESSION OF A **C-KIT**-W-42 MINIGENE IN TRANSGENIC MICE RECAPITULATION OF W PHENOTYPES AND EVIDENCE FOR **C-KIT** FUNCTION IN MELANOBLAST PROGENITORS.
AU RAY P; HIGGINS K M; TAN J C; CHU T Y; YEE N S; NGUYEN H; LACY E; BESMER P
CS MOL. BIOL. PROGRAM, SLOAN KETTERING INST., CORNELL UNIV. GRADUATE SCH. MED. SCI., NEW YORK, NEW YORK 10021.
SO GENES DEV, (1991) 5 (12A), 2265-2273.
CODEN: GEDEEP. ISSN: 0890-9369.
FS BA; OLD

LA English
AB The **proto-oncogene c-kit** encodes a transmembrane tyrosine kinase receptor that is allelic with the murine white-spotting locus (W). W mutations affect melanogenesis, gametogenesis, and hematopoiesis during development and adult life, and they result from the partial or complete loss of **c-kit** function. The W42 allele is a W mutation with severe effects in both the homozygous and the heterozygous states. Previous analysis of the W42 allele identified a missense mutation in an essential amino acid of the c-kitW42 kinase domain that abolishes the in vitro kinase activity of the c-kitW42 protein but does not affect its normal expression. These results suggested that the c-kitW42 allele was a dominant negative mutation within the context of **c-kit**-mediated signal transduction. To further explore the dominant negative characteristics of the W42 mutation, we have generated transgenic mice in which ectopic expression is driven by the human .beta.-actin promoter (hAP). Two mouse lines carrying the hAP-c-kitW42 transgene show an effect on **pigmentation** and the number of tissue mast cells. The patchy coat color pattern of the line 695 mice may reflect variable expression of the transgene in melanoblast progenitors and their descendents and, consequently, is indicative of a function for **c-kit** in early melanoblasts. Germ cell development and erthyropoiesis, however, do not appear to be affected by the transgene. Mice expressing the c-kitW42 transgene therefore recapitulate some of the phenotypes of mice with W mutations. These results are therefore in agreement with the molecular basis of the W42 mutation and the dominant-negative characteristics of the c-kitW42 protein product.

L66 ANSWER 69 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1991:450525 BIOSIS
DN BA92:95305
TI SIMPLE ALLERGEN SKIN TEST DEVICE MULTI **SKIT** TENTATIVE NAME.
AU MIYANO M; KATO Y; OTSUKA T; SAEKI N; TOKUDA Y
CS DEP. DERMATOL., TOKYO MED. COLL., TOKYO, JAPAN.
SO JPN J ALLERGOL, (1991) 40 (6), 611-619.
CODEN: ARERAM. ISSN: 0021-4884.
FS BA; OLD
LA Japanese
AB We have developed a device tentatively named Multi **Skit** (Mu), a simple allergen test device, in order to conduct the skin test safely, accurately and conveniently. The utility of this device was evaluated by determining how the results obtained by the intradermal test (In) and Mu were correlated with those obtained by IgE RAST (RA) in 65 AD patients. RA values concerning nine antigens were compared to results obtained by the In and Mu in terms of the positve and negative response coincidence rates, overall coincidence rates, and false-positive and false-negative response rates. The correlation between RA data obtained from the literature and the results of the scratch test (Sc) was also evaluated. The results of In and RAST values showed no correlation regardless of the food antigen used. Mu and RAST values showed correlation with respect to all 4 food antigens except soy-bean, resulting in overall coincidence rates of 66.2% to 87.7%, which were higher than those concerning the Sc. With respect to false-positive response to environmental antigens, the rate obtained by Mu was higher than that by the Sc, but it was lower than than by the In. However, Mu was the most excellent test with respect to the other indices, i.e., positive and negative response coincidence rates, overall coincidence rates (73.9.apprx.89.2%) and false-negative responses. The mechanism of Mu makers it possible to minimize variations from one investigator to another, and the major drawbacks of all other skin tests. Mu is a safe and convenient screening skin test device which provides accurate and specific test results.

=> fil wpix

FILE 'WPIX' ENTERED AT 09:49:41 ON 09 FEB 2001

FILE LAST UPDATED: 07 FEB 2001 <20010207/UP>
>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK 200108 <200108/DW>
DERWENT WEEK FOR CHEMICAL CODING: 200108
DERWENT WEEK FOR POLYMER INDEXING: 200108
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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=> d his l67-

(FILE 'BIOSIS' ENTERED AT 09:33:19 ON 09 FEB 2001)

FILE 'WPIX' ENTERED AT 09:36:21 ON 09 FEB 2001
L67 893 S L43
L68 46 S (B04-H16 OR C04-H16)/MC
L69 907 S L67,L68
L70 20 S L69 AND (B14-N17 OR C14-N17 OR B14-N17C OR C14-N17C OR B12-A0
L71 30 S L69 AND (P930 OR P940 OR P941 OR P942 OR P943 OR Q262)/M0,M1,
L72 24 S L69 AND (B14-C03 OR C14-C03 OR B12-D07 OR C12-D07)/MC
L73 47 S L70-L72
L74 46 S L73 NOT LONGLEY B?/AU
L75 10 S L74 AND L68
L76 30 S L74 AND STEM CELL FACTOR
L77 0 S L74 AND PROTO ONCOGENE
L78 15 S L74 AND (CKIT OR C KIT)
L79 46 S L75,L76,L78
L80 30 S L79 AND STEM CELL FACTOR
L81 10 S L79 AND L68
L82 32 S L80,L81
L83 14 S L79 NOT L82

FILE 'WPIX' ENTERED AT 09:49:41 ON 09 FEB 2001

=> d all abeq tech tot l82

L82 ANSWER 1 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-071273 [08] WPIX
DNN N2001-053932 DNC C2001-019975
TI Siah-Mediated Degradation Protein, useful for drug screening, for therapeutic applications and for functional genomics.
DC B04 D16 P14 S03
IN MATSUZAWA, S; REED, J C
PA (BURN-N) BURNHAM INST
CYC 93
PI WO 2000077207 A2 20001221 (200108)* EN 121p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
ADT WO 2000077207 A2 WO 2000-US15873 20000609
PRAI US 1999-330517 19990611
IC ICM C12N015-12
ICS A01K067-027; A61K038-17; A61K039-395; A61K048-00; C07K014-47;

C07K016-18; C07K019-00; C12N005-10; C12N015-00; C12N015-11; C12N015-62; C12Q001-68; G01N033-68

AB WO 200077207 A UPAB: 20010207

NOVELTY - Isolated nucleic acid (I) encoding a Siah-Mediated Degradation Protein (SMDP) and/or Skp1 Cullin F-box (**SCF**)-complex protein (SCP), or their functional fragment, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a vector (II) and a recombinant cell (III), containing (I);

(2) an oligonucleotide (Ia) comprising at least 15 nucleotides capable of specifically hybridizing to a nucleotide sequence (S1) comprising 1274, 1432, 1413, 1673, 1892, 1075 or 2037 nucleotides fully defined in the specification;

(3) an antisense-nucleic acid (Ib) capable of specifically binding to mRNA encoded by (I);

(4) a kit for detecting the presence of SMDP and/or SCP cDNA sequence, comprising (Ia);

(5) an isolated SMDP and/or SCP characterized by its ability to bind at least one SMDP and/or SCP;

(6) expressing SMDP and/or SCP;

(7) an isolated anti-SMDP and/or SCP antibody (Ab) having specific reactivity with SMDP and/or SCP;

(8) a composition comprising (Ib) effective to inhibit expression of human SMDP and/or SCP and an acceptable hydrophobic carrier capable of passing through a cell membrane;

(9) a transgenic non-human mammal expressing (I);

(10) identifying (I) by contacting a sample containing nucleic acid with (Ia) under high stringency hybridization conditions, and identifying the compounds that hybridize;

(11) detecting the presence of human SMDP and/or SCP in a sample by contacting a test sample with Ab and detecting the presence of Ab-SMDP and/or SCP complex to detect the presence of SMDP and/or SCP in the sample;

(12) single strand DNA primers for amplification of (I), comprising a nucleic acid sequence derived from S1;

(13) a bioassay for evaluating whether test compounds are capable of acting as agonists or antagonists for SMDP and/or SCP protein or their functional fragments, involving culturing of cells containing (I) in the presence of a test compound whose ability to modulate activity of SMDP and/or SCP such as protein:protein binding activity or protein degradation activity, is sought to be determined, and monitoring the cells for either an increase or decrease in the level of protein activity;

(14) a therapeutic composition (TC) comprising SMDP and/or SCP, their functional fragments, a compound identified the above said method, or Ab;

(15) inducing the degradation function of a target protein, by expressing a chimeric protein (CP) comprising a target-protein binding domain operatively linked to a protein degradation binding domain of a protein unit of the ubiquitin-mediated protein degradation family, in a cell;

(16) determining the function of a target protein, by expressing CP in a first cell, and comparing its phenotype to the phenotype of a control second cell;

(17) identifying a nucleic acid molecule encoding a protein that modulates a cellular phenotype, by expressing a chimeric nucleic acid comprising a unit of nucleic acid library fused to nucleic acid encoding a protein degradation binding domain of a protein unit of the ubiquitin-mediated protein degradation family, in a cell, and screening the cell for the modulation of the phenotype;

(18) a chimeric nucleic acid screened by the above said method;

(19) a nucleic acid library comprising a number of chimeric nucleic acids such that each chimeric nucleic acid comprises an SMDP and/or SCP or its functional fragment;

(20) treating a disease by degrading the function of a target protein, by introducing CP into a cell; and

(21) a chimeric protein comprising SMDP and/or SCP.

ACTIVITY - Cytostatic; antiinflammatory; antiarthritic;

immunosuppressive; antibacterial.
No supporting data given.
MECHANISM OF ACTION - Modulator of SMDP and/or SCP activity.
No supporting data given.
USE - SMDP and/or SCP are useful for modulating the activity of oncogenic proteins. Agonists or antagonists of SMDP and/or SCP protein are useful for modulating the activity of SMDP and/or SCP protein as well as modulating protein degradation mediated by SMDP and/or SCP protein. TC is useful for treating a pathology characterized by abnormal cell proliferation and inflammation. (I) is useful as a probe for assaying the presence and/or the amount of SMDP and/or SCP gene or mRNA transcript in a given sample. (I) and (Ia) are also useful as primers and/or templates in PCR (polymerase chain reaction) for amplifying (I). SMDP and/or SCP proteins are useful in bioassays, and as immunogens for producing Ab. Bioassays are useful for monitoring SMDP and/or SCP levels and for diagnosing physiological disorders that result from abnormal levels of SMDP and/or SCP. SMDP and/or SCP are useful for treating cancer pathologies, keratin hyperplasia, keloid, neoplasia, benign prosthetic hypertrophy, inflammatory hyperplasia, bone marrow aplasia, immunodeficiencies and inflammatory diseases such as sepsis, fibrosis, arthritis and graft versus host diseases.
Dwg.0/10

FS CPI EPI GMPI
FA AB; DCN
MC CPI: B04-B03C; B04-C01G; B04-E03; B04-E05; B04-E06; B04-E08; B04-G01; B04-G21; B04-G22; B04-P01A0E; B11-C08E5; B12-K04F; B14-A01; **B14-C03**; B14-C09; B14-G02; B14-H01; D05-H09; D05-H11; D05-H12A; D05-H12C; D05-H12D1; D05-H12D2; D05-H17A; D05-H17C
EPI: S03-E14H
TECH UPTX: 20010207
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Sequence: (I) comprises a DNA encoding an amino acid sequence comprising 298, 228, 80, 443, 522, 327 or 447 amino acids fully defined in the specification, a DNA that hybridizes to the above DNA under moderately stringent conditions and encoding biologically active SMDP and/or SCP, or a DNA degenerate with respect to either of the above sequences and encoding a biologically active SMDP and/or SCP. (I) comprises a sequence that hybridizes under high stringent conditions to the SMDP and/or SCP coding portion of S1. (Ia) is labeled with detectable marker. Ab is a monoclonal or polyclonal antibody. (I) is Sia-1alpha, SIP-L, SIP-S, SAF-1, SAF-2, and SAD, or their functional fragments.
Preferred Method: (I) has been mutated and SMDP and/or SCP so expressed is not native to SMDP and/or SCP. Activity of SMDP and/or SCP is modulated by binding of Siah-1 to APC. The transgenic non-human animal expressing (I) is a mouse. (I) which modulates the phenotype such as cell proliferation, cell survival, cell death, cell secretion or cell migration, is screened.

L82 ANSWER 2 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-049933 [06] WPIX
DNC C2001-013747
TI Purified human amniotic epithelial cells, useful e.g. in gene therapy and wound repair, are derived from placenta and can substitute for embryonic stem cells.
DC B04 D16 D22
IN GOLDSTEIN, A L; HU, V W; PRESTIDGE, P D; SACKIER, J M; WIGGINTON, G
PA (LIFE-N) LIFEBANK SERVICES LLC
CYC 93
PI WO 2000073421 A2 20001207 (200106)* EN 24p C12N005-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
ADT WO 2000073421 A2 WO 2000-US40052 20000601
PRAI US 1999-137740 19990602

IC ICM C12N005-00
AB WO 200073421 A UPAB: 20010126
NOVELTY - Purified human amniotic epithelial cells (A), prepared from placenta, characterized by a round, cobblestone morphology, large nuclei, cytokeratin, epithelial membrane antigen and gap junction communication, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method for obtaining (A);
(2) cryopreservation of human amniotic tissue from placenta by freezing in a solution that contains a cryoprotective agent (I);
(3) cryopreservation of (A); and
(4) reconstructive treatment of tissues by administering growth factors, cytokines or other biological response modifiers derived from (A).
ACTIVITY - Cardiant; vulnerary; cytostatic.
No supporting biological data given.
MECHANISM OF ACTION - Gene therapy.
USE - For treatment of lysosomal storage diseases, e.g. Tay-Sachs, Fabry or Gaucher diseases or mucopolysaccharidosis, by enzyme replacement, inborn metabolic errors that affect e.g. the cardiovascular, respiratory, gastro-intestinal etc. systems (by transplanting (A) that have been transformed with specific genes), cancer (using the cells as carriers for autologous or heterologous transgenes), corneal epithelial defects, cartilage damage or facial dermoabrasion (by replacing or regenerating damaged tissue, e.g. where applied as burn or wound dressing or introduced by surgical implantation for reconstruction). Growth factors, cytokines and other biological response modifiers secreted by (A) can also be used for reconstructive treatment of tissue, in vivo or in vitro.
ADVANTAGE - (A) can now be produced from readily available placental tissue, avoiding ethical problems associated with use of embryonic stem cells.
Dwg.0/2
FS CPI
FA AB; DCN
MC CPI: B04-F02; B04-F0200E; B11-C09; B14-E10; B14-F01; B14-F02; B14-H01; B14-K01; B14-N17B; **B14-N17C**; B14-S03; D05-H14B2; D09-C
TECH UPTX: 20010126
TECHNOLOGY FOCUS - BIOLOGY - Preparation: (A) are isolated from placental amniotic tissue and particularly freed from mesenchymal fibroblasts by treatment with dispase and trypsin/ethylenediamine tetra-acetic acid and selective adhesion to plastics. (A) may then be cultured, e.g. in Dulbecco's modified Eagle medium or F12 medium, or in a medium supplemented with fetal bovine, human or umbilical cord serum or growth factors, cytokines, hormones and/or vitamins. (A) may be cultured on feeder cells that are obtained from the same placenta as (A) or from (non-)human sources, particularly on irradiated fibroblasts. (A) may also be expanded in presence of an agent that suppresses cellular differentiation, e.g. leukemia inhibitory factor or **stem cell factor**. Optionally (A) are used to establish stable cell lines by exposure to a chemical carcinogen and these cells can be expanded, cryopreserved and/or thawed. These cell lines may be exposed to a differentiation-inducing agent (II) and differentiation analyzed by staining with tissue-specific antibodies.
Preferred Process: Cryopreservation comprises flash-freezing, e.g. by immersing a vessel that contains the tissue or cells in a solution containing (I) in liquid nitrogen or controlled-rate freezing. Where tissue is frozen, it may be subsequently thawed and (A) isolated from it. (A) are cultured and assessed for viability, proliferative potential and/or longevity, e.g. by trypan blue exclusion or uptake of fluorescein diacetate or propidium iodide, thymidine uptake, MTT proliferation or the number of population doublings in extended culture.
Preferred Materials: (I) are dimethylsulfoxide or glycerol and typical (II) include insulin, hydrocortisone, interleukin-1alpha, retinoic acid.

L82 ANSWER 3 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 2000-672494 [65] WPIX
DNN N2000-498611 DNC C2000-203620
TI Mineralization and cellular patterning on biomaterial surfaces useful cell culture, cell transplantation, tissue engineering and guided tissue regeneration.
DC A18 A23 A96 B04 D16 G06 P34
IN KOHN, D H; MOONEY, D J; MURPHY, W L; PETERS, M C
PA (UNMI) UNIV MICHIGAN
CYC 91
PI WO 2000056375 A2 20000928 (200065)* EN 78p A61L027-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000041730 A 20001009 (200103) A61L027-00
ADT WO 2000056375 A2 WO 2000-US7207 20000317; AU 2000041730 A AU 2000-41730 20000317
FDT AU 2000041730 A Based on WO 200056375
PRAI US 1999-167289 19991124; US 1999-125118 19990319
IC ICM A61L027-00
AB WO 200056375 A UPAB: 20001214
NOVELTY - Surface-modification of a biocompatible material comprising generating a patterned surface on a biocompatible material by irradiating a photosensitive surface of a biocompatible material with pre-patterned electromagnetic radiation, generating a pattern on the surface of the biocompatible material, is new.

DETAILED DESCRIPTION - Surface-modification of a biocompatible material comprising generating a patterned surface on a biocompatible material by irradiating a photosensitive surface of a biocompatible material with pre-patterned electromagnetic radiation, generating a pattern on the surface of the biocompatible material, is new. The method alternatively comprises generating an extended mineralized surface on a biocompatible material by functionalizing a surface of a biocompatible material and contacting the functionalized surface with a mineral-containing solution, generating extended mineralization on the surface of the biocompatible material.

INDEPENDENT CLAIMS are also included for the following:

(1) a surface-modified biocompatible material comprising a modified surface prepared by the novel method;

(2) a cell culture device, and implantable biomedical device, comprising the material of (1); and

(3) a method of culturing cells, comprising growing a cell population in contact with the material of (1).

USE - The surface-modified biocompatible material is useful in cell culture, cell transplantation, tissue engineering and guided tissue regeneration. The surface-modified biocompatible material is useful in a cell culture or implantable biomedical device. In particular, the surface-modified biocompatible material is useful for generating bone-like tissue and neovascularized or vascularized tissue. The patterned/mineralized biomaterials provide more control over ongoing biological processes, such as mineralization, growth factor release, cellular attachment and tissue growth. (All claimed).

ADVANTAGE - The biocompatible materials of the invention provide orthopedic scaffolds that combine the degradability, biocompatibility and osteoconductivity of mineralized scaffolds with the tissue inductive properties of bioactive polypeptides. Patterning provides an additional degree of control. The invention achieves the growth of bone-like mineral on the inner pore surfaces of a scaffold containing a growth factor without compromising factor bioactivity or scaffold porosity.

Dwg.0/9
FS CPI GMPI
FA AB; DCN
MC CPI: A12-V01; A12-W11L; B04-C01; B04-C03; B04-E01; B04-F01; B04-F02; B04-H02; B04-H04; B04-H05; B04-H06; **B04-H16**; B04-J01;

B04-J10; B04-L01; B04-N02; B11-A; B11-C04A; B11-C09; B14-A01; B14-A02; B14-E11; B14-H01; B14-J01; B14-N01; B14-N17B; B14-S03; D05-H02; D05-H10; G06-D04; G06-E04; G06-G18

TECH UPTX: 20001214

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: A patterned surface is generated on a biocompatible material by functionalizing a photosensitive surface by irradiation with a pre-patterned electromagnetic radiation. The pre-patterned radiation is constructively and destructively interfering electromagnetic radiation or radiation in the visible, ultraviolet (UV) or infrared spectrum. It may be generated by impinging monchromatic radiation on a diffractive optical element that converts the radiation into constructively and destructively interfering radiation. The monochromatic radiation is generated by a laser, a mercury bulb, or from an electromagnetic radiation source, in combination with a filter. The diffractive optical element is a diffractive lens, a deflector/array generator, a hemisphere lenslet, a kinoform, a diffraction grating, a fresnel microlens, or a phase-only hologram. The element may be made of transparent polymer or glass. The diffraction grating is made of metal on glass, metal on polymer or metal with transmission apertures. The pattern generated comprises a pattern with a resolution of 1-500, preferably 1-10 or 10-20 micro-M. The biocompatible material is preferably a naturally occurring polymer chosen from collagen, alginate, fibrin, matrigel, modified alginate, elastin, chitosan and gelatin. Alternatively it is a synthetic polymer. Preferred biocompatible materials comprise a polylactic-co-glycolic acid (PLG) co-polymer biomaterial having a ration of 85 % lactide to 15 % glycolide. A bioactive substance may be operatively associated with the biocompatible material during a gas foaming and particulate leaching process. The bioactive substance may be a drug or cell or DNA, RNA, protein, etc. Cells are cultured by contacting the cell population with the surface-modified biocompatible material, especially under conditions to generate a two or three-dimensional tissue-like structure. The photosensitive composition comprises a photoinitiator, preferably a visible light or UV excitable photoinitiator, and a polymerizable component.

TECHNOLOGY FOCUS - POLYMERS - Preferred Element: The diffractive optical element is made of a transparent polymer selected from poly(methyl methacrylate), poly(styrene) or a high density poly(ethylene).

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Element: The diffractive optical element is made of fused silica or sapphire. Preferred Photoinitiator: The UV-excitable photoinitiator is a benzoin derivative, benzil ketal, hydroxyalkylphenone, alpha-amino ketone, acylphophine oxide, benzophenone derivative, or a thioxanthone derivative. The visible light excitable photoinitiator is eosin, methylene blue, rose bengal, dialkylphenacylsulfonium butyltriphenylborate, a fluorinated diacyltitanocene, a cyanine, a cyanine borate, a ketocoumarin or a fluorononе dye.

L82 ANSWER 4 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-531685 [48] WPIX
CR 1996-010869 [01]; 1997-052228 [05]; 2000-430414 [36]
DNC C2000-158532
TI Chemotactic polynucleotide useful for myeloprotection, neuronal protection, treating tumors, regulating hematopoiesis and for diagnosing conditions associated with expression of chemotactic polypeptide.
DC B04 D16
IN LI, H; RUBEN, S M; SUTTON, G
PA (HUMA-N) HUMAN GENOME SCI INC
CYC 1
PI US 6100389 A 20000808 (200048)* 33p C12N001-20
ADT US 6100389 A CIP of WO 1994-US5384 19940516, CIP of US 1995-424425 19950421, CIP of US 1995-479126 19950607, US 1998-44855 19980320
PRAI US 1998-44855 19980320; WO 1994-US5384 19940516; US 1995-424425 19950421; US 1995-479126 19950607
IC ICM C12N001-20

ICS C12N005-10; C12N015-12; C12N015-19
AB US 6100389 A UPAB: 20001001
NOVELTY - An isolated human chemotactic polynucleotide (I), comprising 20, 30 or 25 contiguous nucleotides of a sequence (S1) of 360 bp (or its complement), encoding a polypeptide of at least 30 contiguous amino acids of a sequence of 119 amino acids defined in the specification, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a vector comprising (I); and
(2) an isolated polynucleotide (II) comprising nucleotides 79-357 of S1 (or its degenerate variant).
ACTIVITY - Cytostatic; Vulnerary.
The myeloprotective effect of chemotactic polypeptide (CP) against cytosine Arabinoside (Ara-C) was tested. Lin-cells were plated in a growth medium supplemented with mouse interleukin-3 (5 ng/ml), mouse **stem cell factor** (**SCF**) and CP (100 ng/ml). After 48 hours of incubation, Ara-C (50 mu l/ml) was added to the cultures. After a day, cells were harvested, washed with HBSS (Hank's Balanced Salt Solution) to remove the drug and cytokines and assayed for the presence of high proliferative potential colony forming cells (HPP-CFC) and low proliferative potential colony forming cell (LPP-CFC). Percentage protection was calculated. The results showed that CP protected HPP-FCF but not LPP-CFC from the cytostatic effect of Ara-C.
MECHANISM OF ACTION - Chemotaxis-stimulator.
USE - (I) is useful for stem cell mobilization, myeloprotection and neuronal protection, to treat tumors, to promote wound healing, to combat parasitic infection and to regulate hematopoiesis. The nucleic acid is useful for diagnosis of diseases or susceptibility to a disease resulting from under- expression of chemotactic polypeptide. (I) is also useful as a research reagent and for in vitro synthesis of DNA and manufacture of DNA vectors. Fragments of (I) are used as hybridization probes for a cDNA library to isolate the full-length cDNA.
Dwg.0/10
FS CPI
FA AB; DCN
MC CPI: B04-C01F; B04-C01G; B04-E03; B04-E05; B04-E08; B11-C08E5; B12-K04A; B12-K04F; B14-B02; B14-H01; **B14-N17**; D05-H09; D05-H12A; D05-H12D1; D05-H12E; D05-H17A
TECH UPTX: 20001001
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polynucleotide: (I) is a double or single stranded DNA or RNA and further comprises a heterologous polynucleotide encoding a heterologous polypeptide. (I) is 50 or 60 nucleotides in length and comprises 50 or 60 contiguous nucleotides of S1. (I) encodes a polypeptide which inhibits growth or differentiation of high proliferative potential colony forming cells (HPP-CFC) in vitro or increases the frequency of hematopoietic progenitor cells in peripheral blood when injected intraperitoneally or intravenously into a mouse. (II) comprises nucleotides 4-357 of S1 or its degenerate variants.

L82 ANSWER 5 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-452289 [39] WPIX
CR 2000-482592 [39]
DNC C2000-137860
TI Pharmaceutical composition for the sustained-release of a biologically active agent (BAA), such as granulocyte-colony stimulating factor, comprises incorporating the BAA into a biocompatible polyol/oil suspension.
DC B04 D16
IN BEEKMAN, A C; GOLDENBERG, M S; SHAN, D
PA (AMGE-N) AMGEN INC
CYC 89
PI WO 2000038652 A1 20000706 (200039)* EN 38p A61K009-10
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS

LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000024838 A 20000731 (200050) A61K009-10
ADT WO 2000038652 A1 WO 1999-US30527 19991220; AU 2000024838 A AU 2000-24838 19991220
FDT AU 2000024838 A Based on WO 200038652
PRAI US 1999-448205 19991123; US 1998-221181 19981223
IC ICM A61K009-10
ICS A61K047-00; A61K047-10; A61K047-12; A61K047-26; A61K047-44
AB WO 200038652 A UPAB: 20000905
NOVELTY - A pharmaceutical composition comprising a biologically active agent (BAA) incorporated into a biocompatible polyol/oil suspension which contains a thickener is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) preparing pharmaceutical compositions of BAA/polyol/oil sustained-release suspensions comprising suspending a BAA in a polyol to form a BAA/polyol mixture which is suspended in a mixture comprising thickened oil to form a BAA/polyol/oil suspension;

(2) parenterally administrating a BAA/polyol/oil suspension to a warm blooded animal subcutaneously or intramuscularly and releasing the active agent from the suspension at a controlled rate for up to one week or more; and

(3) a prefilled syringe containing the new composition.

ACTIVITY - Antiinflammatory.

MECHANISM OF ACTION - None given.

USE - For the sustained-release of a BAA such as interferon consensus, erythropoietin, granulocyte-colony stimulating factor, **stem cell factor**, leptin, tumor necrosis factor-binding protein, interleukin-1 receptor antagonist, brain derived neurotrophic factor, glial derived neurotrophic factor, neutrophic factor 3, osteoprotegerin, granulocyte macrophage colony stimulating factor, megakaryocyte derived growth factor, keratinocyte growth factor, thrombopoietin, or novel erythropoiesis stimulating protein (claimed). For the manufacture of medicaments for the treatment or amelioration of conditions that the BAA is intended to treat.

ADVANTAGE - The release of a medicament can be controlled to provide longer periods of consistent release that previous methods of treatment do not achieve, such as repeated injections. Blood levels of the active ingredient can be controlled, providing an enhanced prophylactic, therapeutic, or diagnostic effect as well as greater safety, patient convenience and patient compliance. The compositions can lead to dose sparing and a lower cost of protein production. Bioavailability and protein protection, stability and potency are increased.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-B01C1; B04-H04; B04-H04A; B04-H06; B04-H07; B04-H08; **B04-H16**; B11-C02; B12-M03; B12-M10A; **B14-C03**; B14-L01; B14-L07; D05-H17A2; D05-H19
TECH UPTX: 20000818
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The biocompatible polyol is glycerol, erythritol, arabinose, xylose, ribose, inositol, fructose, galactose, maltose or sucrose. The thickener is polyvalent metal salts of organic acids, oleaginous materials such as waxes and high viscosity oils, or organic or inorganic fillers such as polymers and salts. The thickener is aluminum monostearate or white wax. The oil is sesame, castor, cottonseed, cannola, saffron, olive, peanut, sunflower seed, alpha-tocopherol, and ethyl oleate. The BAA is interferon consensus, erythropoietin, granulocyte-colony stimulating factor, **stem cell factor**, leptin, tumor necrosis factor-binding protein, interleukin-1 receptor antagonist, brain derived neurotrophic factor, glial derived neurotrophic factor, neutrophic factor 3, osteoprotegerin, granulocyte macrophage colony stimulating factor, megakaryocyte derived growth factor, keratinocyte growth factor, thrombopoietin, or novel erythropoiesis stimulating protein. The BAA is a

small molecule drug. The composition provides for the sustained-release of the BAA.

L82 ANSWER 6 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-442382 [38] WPIX
DNC C2000-134544
TI Expanding human bone marrow CD34+CD38- hematopoietic progenitor cells, including primitive stem cells, for application in gene therapy comprises culturing in the presence of cytokines and human brain endothelial cells.
DC B04 D16
IN CHUTE, D J; CHUTE, J P; DAVIS, T A; SAINI, A A
PA (NAVA-N) NAVAL MEDICAL RES CENT
CYC 87
PI WO 2000036090 A2 20000622 (200038)* EN 35p C12N005-08
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 2000020440 A 20000703 (200046) C12N005-08
ADT WO 2000036090 A2 WO 1999-US28939 19991203; AU 2000020440 A AU 2000-20440 19991203
FDT AU 2000020440 A Based on WO 200036090
PRAI US 1998-112042 19981204
IC ICM C12N005-08
ICS A61K035-28; A61P043-00
AB WO 200036090 A UPAB: 20000811
NOVELTY - Expanding human bone marrow CD34+CD38- hematopoietic progenitor cells (I), including primitive stem cells, in the presence of cytokines and human brain endothelial cells is new.
DETAILED DESCRIPTION - Expanding human bone marrow CD34+CD38- hematopoietic progenitor cells (I), including primitive stem cells, comprises:
(a) contacting isolated (I) with human brain endothelial cells; and
(b) co-culturing (I) and endothelial cells in the presence of at least one cytokine to support amplification/ expansion of the CD34+ stem and progenitor cells.
INDEPENDENT CLAIMS are also included for the following:
(1) engrafting human bone marrow (I) in a human comprising:
(a) contacting isolated (I) with human brain endothelial cells containing a factor which expands (I);
(b) co-culturing (I) and endothelial cells in the presence of at least one cytokine to support amplification/ expansion of (I);
(c) isolating the amplified/ expanded (I) from the culture; and
(d) infusing the cells from step (c) into a human; and
(2) a growth medium for cell expansion comprising human brain endothelial cells and a cytokine selected from granulocyte-macrophage colony stimulating factor, interleukin-3, **stem cell factor**, interleukin-6 and flt3-ligand.
USE - Has direct application in gene therapy, cord blood expansion and stem cell transplantation.
ADVANTAGE - The new method provides CD34+CD38- cells which maintain their phenotype through long term culture. Previous attempts to do this have been unsuccessful due to differentiation and cell death when the cells are exposed to cytokines.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-B04E; B04-F02; B04-H02C; B04-H02G; B04-H04C; **B04-H16**; D05-H01; D05-H08
TECH UPTX: 20000811
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: (I) are preferably isolated from bone marrow of a human prior to being contacted with endothelial cells. The expansion can be carried out either in vitro or ex vivo. (I) is preferably contacted with a semi-confluent monolayer of

endothelial cells. The cytokine is preferably a mixture of granulocyte-macrophage colony stimulating factor, interleukin-3, **stem cell factor** and interleukin-6, especially granulocyte-macrophage colony stimulating factor.
The cells are preferably isolated from the bone marrow of a human in need of (I) and (I) is preferably isolated from the bone marrow of a donor (all claimed). The endothelial cells are preferably human brain derived endothelial cells (HUBECs).
Preferred Growth Medium: The growth medium preferably comprises a cytokine selected from granulocyte-macrophage colony stimulating factor, interleukin-3, **stem cell factor** and interleukin-6 and a monolayer of human brain endothelial cells.

L82 ANSWER 7 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-376528 [32] WPIX
DNC C2000-113930
TI Preparing cells for use in humans, useful for gene therapy or tissue repair, by transfection with growth or differentiation factor then transplanting so that differentiation occurs in vivo.
DC B04 D16
IN HAVEMANN, K; MUELLER, R; SEDLACEK, H
PA (AVET) AVENTIS PHARMA DEUT GMBH
CYC 89
PI WO 2000028010 A2 20000518 (200032)* DE 38p C12N015-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
DE 19850986 A1 20000525 (200032) C12N015-85
AU 2000010407 A 20000529 (200041) C12N015-00
ADT WO 2000028010 A2 WO 1999-EP7902 19991019; DE 19850986 A1 DE 1998-19850986 19981105; AU 2000010407 A AU 2000-10407 19991019
FDT AU 2000010407 A Based on WO 200028010
PRAI DE 1998-19850986 19981105
IC ICM C12N015-00; C12N015-85
AB WO 200028010 A UPAB: 20000706
NOVELTY - Preparation of cells (A) suitable for treating humans comprises transfecting human cells in vitro with at least one gene (I) encoding a growth and/or differentiation factor (II), or the corresponding receptor, under control of a promoter. The transfected cells are able, after return to the body, to differentiate in the required fashion.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for cells produced this way.
ACTIVITY - Angiogenic; anti-inflammatory; anticancer.
MECHANISM OF ACTION - Cell replacement.
USE - (A) are used:
(i) as cell vectors in gene therapy; and
(ii) for treatment of endothelial cell defects (e.g. after blood vessel dilation); to stimulate angiogenesis, for healing bones, to promote healing of injuries to the central nervous system, for treating or preventing joint disease, inflammation, autoimmune disease or organ rejection, and to assist inflammatory and rejection responses in cases of infection and cancer.
ADVANTAGE - Transfection in vitro of undifferentiated cells overcomes the problem of transplanting differentiated cells, which are often strongly adherent and can not easily be formulated as suspensions without compromising their function or survival. The growth and differentiation of implanted cells may be regulated by appropriate choice of promoter.
Dwg.0/1
FS CPI
FA AB; DCN
MC CPI: B04-E02B; B04-E02D; B04-E03B; B04-E03D; B04-F02; B04-F0200E; **B14-C03**; B14-C09; B14-G02C; B14-G02D; B14-H02; B14-J01; B14-N01; B14-N17B; B14-S03; D05-H12A; D05-H14

TECH UPTX: 20000706
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Process: When returned to the body, (A) become integrated into tissue. The gene for (II) and/or its receptor is transfected as part of a nucleic acid construct which may additionally contain sequences encoding prophylactic or therapeutic proteins or enzymes involved in prodrug conversion. The promoter is activatable in a cell or cell-cycle specific manner, metabolically or pharmacolgically.
Preferred Cells: These are mononuclear cells (from blood, blood vessels, umbilical cord or placenta, particularly carrying the surface markers CD11, 13, 14, 34 and 68); a suspension of cells from bone marrow, spleen, lymph node, peritoneum or pleura; cells from lymph or connective tissue fluid, or endothelial cells or fibroblasts.
Preferred Materials: Many suitable (II) for particular applications are listed, e.g:
(i) for differentiation to endothelial cells, vascular endothelial growth factor, interleukin (IL)-1 or -8, or **stem cell factor**;
(ii) for differentiation to osteoblasts, bone morphogenic proteins 1-8;
(iii) for differentiation to glial cells, glial growth factor or ciliary neurotrophic factor;
(iv) for differentiation to synovial cells, transforming growth factor beta, IL-6 or -10, or superoxide dismutase;
(v) for differentiation to inflammation-inhibiting cells, interferons, IL-4 or -6, or tumor necrosis factor; and
(vi) for differentiation to cells involved in inflammation, IL-1 or -2, granulocyte-macrophage colony-stimulating factor etc.

L82 ANSWER 8 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-376518 [32] WPIX
DNC C2000-113920
TI Serum free medium for cell culture, containing growth factors, lipids, and fatty acids, use particularly for chondrocyte and mesenchymal stem cells for cartilage and bone, avoids risk of serum pathogens.
DC B04 D16 D22
IN CANCEDDA, R; DOZIN, B
PA (CONS-N) CONSORZIO GESTIONE CENT BIOTECNOLOGIA; (NARI-N) IST NAZ RICERCA SUL CANCRO
CYC 90
PI WO 2000027996 A1 20000518 (200032)* EN 17p C12N005-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000013804 A 20000529 (200041) C12N005-00
ADT WO 2000027996 A1 WO 1999-EP8482 19991108; AU 2000013804 A AU 2000-13804 19991108
FDT AU 2000013804 A Based on WO 200027996
PRAI US 1998-107646 19981109
IC ICM C12N005-00
AB WO 200027996 A UPAB: 20000706
NOVELTY - Serum free cell culture medium, comprising one or more growth factors, one or more sources of lipids and fatty acids, in a minimum essential basic medium.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a composition for the expansion of chondrocytes, comprising fibroblast growth factor (FGF)-2, a fatty acid source, ascorbic acid, dexamethasone and insulin;
(2) a composition for the expansion of chondrocytes, comprising a minimum essential medium, epidermal growth factor (EGF), platelet derived growth factor (PDGF)bb, FGF-2, ascorbic acid, linoleic acid, human serum albumin (HSA), beta -mercaptoethanol, dexamethasone, insulin, and human holo- and apo- transferrin;

(3) a composition for the maintenance of mesenchymal stem cells, comprising selenium, biotin, sodium pantotenate, leukemia inhibitory factor (LIF), **stem cell factor (SCF**), and insulin-like growth factor (IGF)-1; and

(4) a composition for the maintenance of mesenchymal stem cells, comprising a minimum essential medium, EGF, PDGFbb, FGF-2, LIF, **SCF**, IGF-1, ascorbic acid, cholesterol, HSA, beta -mercaptoethanol, dexamethasone, human holo- and apo-transferrin, selenium, biotin, and sodium pantotenate.

USE - The compositions are used for growth and proliferation or chondrocytes which are specific for cartilage, and mesenchymal stem cells which can be used for the replacement of bone, cartilage, and other tissues.

Dwg.1/1

FS CPI
FA AB; GI; DCN
MC CPI: B01-B02; B01-D02; B03-F; B04-B01B; B04-B04D2; B04-F01; B04-H06; B04-J03A; B04-N02; B05-B02C; B06-F03; B10-C04E; B14-H02; B14-N01; D05-H01; D05-H08; D09-C01D
TECH UPTX: 20000706

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Components: The lipid or fatty acid is cholesterol or linoleic acid. The serum free medium may also contain steroids, preferably dexamethasone, albumin, preferably HSA, an iron source, preferably transferrin, especially human holo- or apo-transferrin (hHT and hAT), antioxidant, preferably beta-mercaptoethanol or ascorbic acid, trace elements, preferably selenium, vitamins, preferably biotin or pantotenate, and a supplement for coenzyme transport in carboxy group transfer reactions, preferably biotin.

L82 ANSWER 9 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-303778 [26] WPIX
DNN N2000-226931 DNC C2000-092297
TI Nucleic acid encoding an interleukin-17 (IL-17) homolog polypeptide which enhances hematopoiesis, useful for treating e.g. anemia, thrombocytopenia, viral and bacterial infections .
DC B04 D16 P14 S03
IN GLASEBROOK, A L; LIU, L; SU, E W; WEI, J
PA (ELIL) LILLY & CO ELI
CYC 87
PI WO 2000020593 A1 20000413 (200026)* EN 104p C12N015-19
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9962777 A 20000426 (200036) C12N015-19
ADT WO 2000020593 A1 WO 1999-US22678 19990930; AU 9962777 A AU 1999-62777 19990930
FDT AU 9962777 A Based on WO 200020593
PRAI US 1999-138910 19990611; US 1998-102883 19981002; US 1998-110405 19981201
IC ICM C12N015-19
ICS A01K067-027; A61K037-70; A61K038-19; C07K014-52; C07K016-24; C12N005-10; C12Q001-68; G01N033-68
AB WO 200020593 A UPAB: 20000531

NOVELTY - A defined, isolated, nucleic acid (I) (nucleotides 55-591 of a 591 base pair (bp) sequence) encoding an interleukin (IL)-17 homolog polypeptide (II) (amino acids 19-197 of a 197 amino acid sequence), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method for obtaining (I) using a sequence which hybridizes to (I);

(2) a vector comprising (I);

(3) a host cell containing the vector of (2);

(4) the isolated IL-17 homolog polypeptide (II);
(5) a composition comprising (II);
(6) an antibody (Ab) which binds to an epitope of (II);
(7) a host cell expressing the Ab of (6);
(8) a method for producing the Ab comprising culturing the host cell of (7);
(9) a method of producing (II) comprising translating (I);
(10) a transgenic or chimeric non-human animal comprising the host cell of (3);
(11) a method for stimulating hematopoiesis in a cell, tissue, organ or animal comprising contacting with (II);
(12) a method for stimulating the production of neutrophils, granulocytes, or megakaryocytes in a mammal using (II); and
(13) a method for identifying compounds that bind (II).

ACTIVITY - Cytostatic; antianemic; cardiant; hemostatic; anti-inflammatory; anti-HIV (human immunodeficiency virus).

MECHANISM OF ACTION - IL-17 stimulates hematopoiesis.

cDNA encoding IL-17 was cloned into the BamHI and EcoRI sites of pLZRS/IB. The DNA was transfected into Phoenix-E cells which were selected in puromycin for 7 days. The cells were then expanded into flasks and virus was harvested. The virus was filtered, aliquoted, stored and then titered on 3T6 cells and was determined to be greater than 106 colony forming units(CFU)/ml. For generation of retroviral mice, Balb/c male mice were injected with fluorouracil followed by killing and isolation of cells. Cells were seeded into wells of a tray and stimulated for 2 days in Iscoves modified Dulbeccos media (IMDM). Following stimulation, cells were transduced with 4 ml of retroviral supernatant in the same media on fibronectin coated plates. Retroviral transduction was repeated after 4 hours and the cells were cultured for 24 hours. The cells were then placed into the same media with blasticidin and selected for 3 days. Following selection in blasticidin, cells were injected via the tail vein into lethally irradiated male Balb/c mice. Control mice received transduced bone marrow cells with vector alone. Some transduced bone marrow cells were also plated out for a CFU assay. Mice were analyzed 18, 24, 40, and 120 days post-transplant for changes in blood chemistry, hematology, bone marrow progenitor content, and histopathology of hematopoietic tissues and compared to control animals. The IL-17 animals generally looked unhealthy and exhibited an average 10% decrease in body weight. Mouse serum was analyzed for IL-17 homolog polypeptide FLAG (not defined) epitope tagged protein by Western blot analysis. Results showed that cells retrovirally transduced with DNA encoding IL-17h increase bone marrow and spleen cellularity, eosinophils, and colony forming cells (CFCs) and decrease lymphocyte production. IL-17h thus modulates hematopoietic cell growth, including the stimulation of proliferation and/or differentiation of at least 1 early or multipotent progenitor committed to at least 1 granulocyte and/or megakaryocyte lineage.

USE - IL-17 stimulates hematopoiesis and production of neutrophils, granulocytes, or platelets, this may be useful during chemotherapy. IL-17 may also be used to treat viral or bacterial infections, immune related diseases, anemia, leukemia, thrombocytopenia, uremia, Von Willebrand disease, postoperative cardiovascular dysfunction, treatment of AIDS (acquired immune deficiency syndrome)-related bone marrow failure, and inflammatory diseases of the gastrointestinal system, joints, and lungs.

Dwg.0/7

FS CPI EPI GMPI
FA AB; DCN
MC CPI: B04-C01G; B04-E03B; B04-E08; B04-F0100E; B04-G02; B04-H02; B04-H04; B04-H07; B04-P01A0E; B11-C08E; B12-K04E; B14-A01; **B14-C03**; B14-E10; B14-F01; B14-F03; B14-G01B; B14-G03; B14-H01; B14-K01; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H14; D05-H16A; D05-H17A2
EPI: S03-E14H
TECH UPTX: 20000531

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: The composition of (5) further comprises at least 1 compound or protein having an activity selected from hematopoietic, erythropoietic, leukopoietic, thrombopoietic, IL-6, IL-8, ICAM-1 (intercellular adhesion molecule-1), IL-11, IL-17 or

TPO (not defined) activity. The composition of (5) further comprises at least 1 compound or protein selected from erythropoietin, IL-3, colony stimulating factor (CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), **stem cell factor (SCF)**,
IL-6, IL-8, IL-11, and IL-17.
Preferred Method: In (11) and (12) the animal is a primate, preferably a human or a monkey and the quantity of IL-17 is 0.001-10 mg/kg. In (11) the hematopoiesis is selected from erythropoiesis, leukopoiesis, and thrombocytopoiesis.

L82 ANSWER 10 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-273125 [24] WPIX
DNC C2000-083484
TI Stabilized protein compositions comprise protein and stabilizing buffer, used to treat or prevent mastitis, metritis or bovine respiratory disease in cattle and to maintain therapeutic levels of protein.
DC B04 C03
IN CANNING, P C; KAMICKER, B J; KASRAIAN, K
PA (PFIZ) PFIZER PROD INC
CYC 30
PI EP 988861 A1 20000329 (200024)* EN 46p A61K038-18
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
AU 9944501 A 20000309 (200024) A61K038-18
JP 2000063264 A 20000229 (200024) 30p A61K009-08
CA 2280449 A1 20000217 (200031) EN A61K038-27
CN 1250668 A 20000419 (200036) A61K038-18
BR 9904150 A 20001226 (200103) A61K038-27
ADT EP 988861 A1 EP 1999-306262 19990806; AU 9944501 A AU 1999-44501 19990816; JP 2000063264 A JP 1999-230853 19990817; CA 2280449 A1 CA 1999-2280449 19990813; CN 1250668 A CN 1999-122020 19990817; BR 9904150 A BR 1999-4150 19990817
PRAI US 1998-96876 19980817
IC ICM A61K009-08; A61K038-18; A61K038-27
ICS A61K009-10; A61K038-00; A61K038-19; A61K039-00; A61K039-385; A61K039-395; A61K047-16; A61K047-18; A61K047-22; A61P015-14; A61P031-00
AB EP 988861 A UPAB: 20000522
NOVELTY - Stabilized protein compositions (I) comprise a protein and a stabilizing buffer. The compositions are capable of maintaining therapeutic levels of the protein for a sustained period of time.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a dosage form of (I) for parenteral administration, where the protein is present in an amount sufficient to provide therapeutic benefit to a mammal for a predetermined period of time;
(2) a stabilized protein composition (II) comprising bovine G-CSF and HEPES buffer and which is capable of providing an extended shelf life of from 3 weeks to 18 months;
(3) a kit for administering (I) to mammals comprising a first container containing the protein and a second container containing the buffer, where when the protein is combined with the buffer, the composition is capable of maintaining therapeutic levels of the protein in the mammal for a sustained period of at least 3 days.
ACTIVITY - Antibacterial; antiinflammatory.
MECHANISM OF ACTION - Granulocyte colony-stimulating.
The in vivo activity of bovine G-CSF formulated in 1M HEPES was compared with control formulation containing 5% mannitol, 10 mM acetate buffer and Tween 80 (RTM: Polysorbate 80) at pH 4.0. For the control formulation, the white blood count (WBC) stayed above threshold value of 200% of baseline level (level associated with protection against infection) for only about 24-30 hours. When bovine G-CSF was formulated in 1M N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), the polymorphonuclear numbers remained above threshold for a minimum of 3 days or 72 hours.
USE - The compositions are used for sustained administration of

proteins such as colony-stimulating factors (G-CSF), somatotropins, cytokines, antibodies and antigens as well as activins, adhesion molecules (L-selectin, CD-18, intercellular adhesion molecule-1), chemokines, chemotactic factors, erythropoeitin, growth factor, inhibins, insulin, interferons (alpha , beta , gamma), interleukins (1-18), leptin, macrophage inflammatory proteins, macrophage migration inhibitor factor, macrophage stimulating protein, neurotrophins, neutrophils inhibitor factor, oncostatins, somatostatins, **stem cell factors**, tumor necrosis factors, thrombopoetins and their cell-associated and soluble receptors. They are used for the treatment or prevention of mastitis, metritis or bovine respiratory disease in cattle (claimed) such as mastitis associated with Staphylococcus aureus, Escherichia coli, Streptococcus uberis, Strep. dysgalactiae, Strep. agalactiae, Klebsiella spp., Corynebacterium spp., bovine respiratory disease associated with infectious bovine rhinotracheitis virus, parainfluenza virus (P13), bovine viral diarrhea virus, Pasteurella haemolytica, P. multocida and Haemophilus somnus, reproductive disorders such as metritis, and bovine diarrhea associated with E. coli and Eimeria spp. as well as infectious diseases of dogs such as pyoderma and respiratory disease in dogs such as kennel cough. They may also be used in cats and dogs to ameliorate chemotherapy-induced myelosuppression and to allow for more aggressive cancer treatment protocols. They are used to treat humans, cattle, swine, horses, goats, sheep, cats and dogs.

ADVANTAGE - The compositions are capable of maintaining therapeutic levels of the protein for a sustained period of time such as at least 3 days in vivo and in vitro. The compositions have extended shelf-lives of 3 weeks-18 months. The compositions are sterile, well tolerated by mammals without induction of appreciable swelling, pain or necrosis at the injection site.

Solutions containing bovine G-CSF (0.1 mg/ml) were prepared in the buffers TES, HEPES and TRICINE at concentrations of 0.1M, 1M and 2M. Each formulation (1 ml) was placed in a 1-ml vial and placed in an oven at 40 deg. C for 9 days. Samples were removed from each vial every 3 days and analyzed by size exclusion high-performance liquid chromatography (SEC-HPLC). The percentage recovery (remaining) of 0.1 mg/ml bovine G-CSF solutions was determined. The percentage recovery at 0, 3, 6 and 9 days, respectively, were as follows (%): HEPES: 0.1M = 100, 15, 9, 5; 1M = 100, 95, 96, 95; 2M = 100, 78, 82, 83; TES: 0.1M = 100, 16, 11, 9; 1M = 100, 85, 97, 93; 2M = 100, 100, 98, 98; and TRICINE: 0.1M = 100, 17, 10, 5; 1M = 100, 85, 79, 70; 2M = 100, 94, 88, 86. The results showed that the presence of buffers significantly maintained the activity of bovine G-CSF for sustained periods from 3-9 days.

DESCRIPTION OF DRAWING(S) - Plot of white-blood cells versus time past injection (hours) for bovine G-CSF formulated in 1M HEPES versus a control formulation.

Dwg.1/29

FS CPI

FA AB; GI; DCN

MC CPI: B04-B04C; B04-G01; B04-H04A; B04-H04B; B04-H07; B04-H08; B04-J03A; B04-J05J; B04-N02; B07-D11; B10-A09B; B10-B01B; B12-M10A; B14-A01; B14-A02; **B14-C03**; B14-E02; B14-K01; B14-K01B; B14-N14; C04-B04C; C04-G01; C04-H04A; C04-H04B; C04-H07; C04-H08; C04-J03A; C04-J05J; C04-N02; C07-D11; C10-A09B; C10-B01B; C12-M10A; C14-A01; C14-A02; **C14-C03**; C14-E02; C14-K01; C14-K01B; C14-N14

TECH UPTX: 20000522

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compositions: In (I), the proteins are colony-stimulating factors (preferred), somatotropins, cytokines, antibodies and antigens, preferably human granulocyte colony-stimulating factor (G-CSF), bovine G-CSF (preferred) or canine G-CSF. The compositions are at physiological pH, preferably 4.0-7.5. The compositions are at physiological temperature. The stabilizing buffer is N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), N-tris-(hydroxymethyl)aminomethane(hydroxymethyl)-methyl-2-aminoethanesulfonic acid (TES) or N-tris-(hydroxymethyl)aminomethane(hydroxymethyl)methylglycine (TRICINE). The sustained period is at least 3 days, preferably in vivo. The G-CSF is present at a concentration of 0.01-6

mg/ml. The stabilizing buffer is present at a concentration of 0.05-2M. The stabilizing buffer is preferably HEPES at a concentration of 1M. In (II), the HEPES buffer is at 0.05-2M, the pH of the composition is 7.5 and the temperature is less than 40 (preferably less than 4) degreesC. Preferred Dosage Form: The protein is bovine G-CSF present at 0.01-5 mg/ml; the stabilizing buffer is HEPES, TES or TRICINE and is especially HEPES at 0.05-2M; the mammal is a cow; the predetermined period of time is at least 3 days and the composition is at a pH of 7.5. The dosage form further comprises surfactant and viscosity modifiers.

L82 ANSWER 11 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-259135 [23] WPIX
CR 1991-119233 [17]; 1995-346090 [45]
DNC C2000-079421
TI Production of hematopoietic cells suitable for administration to a subject using progenitor cells and expanding the cells using **stem cell factor**.
DC B04 D16
IN BOSSELMANN, R A; MARTIN, F H; SUGGS, S V; ZSEBO, K M
PA (AMGE-N) AMGEN INC
CYC 14
PI EP 992579 A1 20000412 (200023)* EN 123p C12N005-06
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
ADT EP 992579 A1 Div ex EP 1990-310899 19901004, EP 1999-122861 19901004
FDT EP 992579 A1 Div ex EP 423980
PRAI US 1990-589701 19901001; US 1989-422383 19891016; US 1990-537198 19900611; US 1990-573616 19900824; WO 1990-US5548 19900928
IC ICM C12N005-06
ICS A61K035-14; A61K035-28
AB EP 992579 A UPAB: 20000516
NOVELTY - A method of making hematopoietic cells suitable for administration to a subject is new and comprises:
(a) obtaining hematopoietic progenitor cells from a donor; and
(b) expanding the cells by adding to the cells a hematopoietically effective dose of a polypeptide product having at least part of the primary structural confirmation and one or more of the biological properties of naturally occurring **stem cell factor** (**SCF**).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method of making hematopoietic cells suitable for administration to a subject to effect hematopoietic recovery in the subject comprising:
(a) obtaining hematopoietic progenitor cells from a donor; and
(b) expanding the cells obtained in (a) by adding the cells a hematopoietically effective dose of a polypeptide product having at least part of the primary structural confirmation and one or more of the biological properties of naturally occurring **stem cell factor** (**SCF**);
(2) a method for making hematopoietic cells suitable for administration to a subject to treat hematopoietic disorders in the subject comprising:
(a) obtaining hematopoietic progenitor cells from a donor; and
(b) expanding the cells obtained in (a) by adding the cells a hematopoietically effective dose of a polypeptide product having at least part of the primary structural confirmation and one or more of the biological properties of naturally occurring **stem cell factor** (**SCF**); and
(3) a method for expanding hematopoietic cells ex vivo comprising:
(a) obtaining hematopoietic progenitor cells from a donor; and
(b) expanding the cells obtained in (a) by adding the cells a hematopoietically effective dose of a polypeptide product having at least part of the primary structural confirmation and one or more of the biological properties of naturally occurring **stem cell factor** (**SCF**).
USE - The method is useful for stimulating primitive progenitor cells

including early hematopoietic progenitor cells which are capable of maturing to erythroid, megakaryocyte, granulocyte, lymphocyte and macrophage cells. **SCF** results in absolute increases in hematopoietic cells of both myeloid and lymphoid lineages. **SCF** is useful for treating a hematopoietic disorder, e.g. bone marrow failure, induced by an infectious disease, HIV Induced Acquired Immunodeficiency Syndrome (AIDS), Kala Azar, miliary tuberculosis, fulminating septicemia, disseminated fungal disease, malaria (claimed), aplastic anemia, paroxysomal nocturnal hemaglobinuria, myelofibrosis, myelosclerosis, osteopetrosis, metastatic carcinoma, acute leukemia, multiple myeloma, Hodgkin's disease, sarcoidosis, primary splenic pancytopenia, vitamin B12 and folic acid deficiency, pyridoxine deficiency, Diamond Blackfan anemia, hypopigmentation disorders such as piebaldism and vitiligo. The method is useful for expanding early hematopoietic progenitors in syngenic, allogenic or autologous bone marrow transplant. **SCF** is useful for enhancing the efficiency of gene therapy based on transfecting hematopoietic stem cells. **SCF** is also useful for combating the myelosuppressive effects of anti-HIV drugs such as AZT and for enhancing hematopoietic recovery after acute blood loss and as a boost to the immune system for fighting neoplasia (cancer).

ADVANTAGE - The method is capable of stimulating early progenitor cells.

Dwg.0/47

FS CPI
FA AB; DCN
MC CPI: B04-F04; B04-H02; B04-H04; **B04-H16**; B14-A01; B14-A02B1; B14-A04; B14-F03; B14-G01; B14-H01; B14-N01; B14-S03; D05-H08
TECH UPTX: 20000516

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The hematopoietic factors had been administered to the subject prior to obtaining the cells of (a) and are obtained from the bone marrow, peripheral blood or cord blood. The hematopoietic cells are selected from dendritic cells, B-lymphocytes, T lymphocytes, basophils, eosinophils, neutrophils, macrophage, platelets, promyelocytes, metamyelocytes, myelocytes, myeloids, myleoblast and erythrocytes. The hematopoietic disorder is bone marrow failure, induced by an infectious disease, HIV Induced Acquired Immunodeficiency Syndrome (AIDS), Kala Azar, miliary tuberculosis, fulminating septicemia, disseminated fungal disease and malaria. The **SCF** polypeptide is selected from amino acids 1-162, 1-164 and 1-165 optionally consisting of N-terminal methionine. The **SCF** polypeptide is selected from amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137. 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164, 2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-189, 1-220 and 1-248 (all amino acid sequences are fully defined in the specification) and the polypeptides optionally consist of an N-terminal methionine. The hematopoietic progenitor cells are exposed to **stem cell factor** in the presence of at least one other cytokine (e.g. IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, MGDF and L1F. The hematopoietic progenitor cells are exposed to **stem cell factor** in the presence of at least one other hematopoietic factor.

TECHNOLOGY FOCUS - POLYMERS - Preferred Method: The **SCF** is covalently conjugated to a polymer (especially polyethylene glycol).

L82 ANSWER 12 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-181780 [16] WPIX
DNN N2000-134195 DNC C2000-056707
TI Modification of blood lymphocyte counts by administration of a homeopathic composition comprising high dilutions of one or more growth factors.
DC B04 P34
IN BREWITT, B A
PA (BREW-I) BREWITT B A
CYC 1
PI US 6024734 A 20000215 (200016)* 53p A61M031-00

ADT US 6024734 A CIP of US 1994-221365 19940331, Cont of US 1995-488722 19950608, CIP of US 1996-710040 19960910, US 1997-855096 19970513
FDT US 6024734 A CIP of US 5629286
PRAI US 1997-855096 19970513; US 1994-221365 19940331; US 1995-488722 19950608; US 1996-710040 19960910
IC ICM A61M031-00
AB US 6024734 A UPAB: 20000330
NOVELTY - A method for modifying blood lymphocyte counts in a patient involves administering a homeopathic composition comprising a molar concentration of 10-6 - 10-100000 (sic) of one or more growth factors.
USE - The method is used to treat chronic viral infections (especially herpes simplex, Epstein-Barr, HIV, papilloma, Coxsackie B, hauta and hepatitis viruses), cancer, diabetes, inflammation, joint and muscle pain, muscle weakness, fatigue, sinus and nasal congestion, breathing difficulties, poor digestion, neuropathy, headaches, reduced mental acuity, poor memory, skin conditions, fitness, weight imbalances and a variety of psychological conditions such as mood swings, depression, anxiety, confusion, anger. The method is also used to increase lean muscle mass while reducing body fat and improve overall health, fitness and mental clarity.
Dwg.0/34
FS CPI GMPI
FA AB; DCN
MC CPI: B04-H02; B04-H04; B04-H05; B04-H06; B04-H07; B04-H08; B12-M07; B12-M11B; B14-A02; B14-C01; **B14-C03**; B14-H01; B14-J01A1; B14-J01A4; B14-J01B4; **B14-N17**; B14-S04
TECH UPTX: 20000330
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition is in the form of a solution, tablet or form suitable for topical application and contains at least two homeopathic potencies selected from 6 C (10-12), 30 C (10-60), 200 C (10-400) or 1M (10-1000), of at least 1 growth factor selected from the group consisting of granulocyte macrophage-colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), macrophage-colony stimulating factor (M-CSF), tumor necrosis factors (TNFalpha and TNFbeta), transforming growth factors (TGFalpha and TGFbeta), epidermal growth factors (EGF), **stem cell factor** (**SCF**), platelet-derived growth factors (PDGF), platelet-derived endothelial cell growth factor, nerve growth factor (NGF), fibroblast growth factors (FGF), insulin-like growth factors (IGF-I and IGF-II), growth hormone, interleukins 1 to 13 (IL-1 to IL-13), interferons alpha, beta and gamma (IFN-alpha, IFN-beta and IFN-gamma), brain-derived neurotrophic factor, neurotrophins 3 and 4, hepatocyte growth factor, erythropoietin, EGF-like mitogens, TGF-like growth factors, PDGF-like growth factors, melanocyte growth factor, mammary-derived growth factor 1, prostate growth factors, cartilage-derived growth factor, chondrocyte growth factor, bone-derived growth factor, osteosarcoma-derived growth factor, glial growth-promoting factor, colostrum basic growth factor, endothelial cell growth factor, tumor angiogenesis factor, hematopoietic stem cell growth factor, B-cell stimulating factor 2, B-cell differentiation factor, leukemia-derived growth factor, myelomenocytic growth factor, macrophage-derived growth factor, macrophage-activating factor, erythroid-potentiating activity, keratinocyte growth factor, ciliary neurotrophic growth factor, Schwann cell-derived growth factor, vaccinia virus growth factor, bombyxin, neu differentiation factor, v-Sis, glial growth factor/acetylcholine receptor-inducing activity, transferrin, bombesin and bombesin-like peptides, angiotensin II, endothelin, atrial natriuretic factor (ANF) and ANF-like peptides, vasoactive intestinal peptide, and Bradykinin, preferably IGF-1, PDGFBB, TGFbeta1, GM-CSF or NGF, more preferably IGF-1 at a homeopathic potency of 1 M, PDGFBB at 30 C or 1 M, TGFbeta1 at 30 C or 1 M, GM-CSF at 200 C or NGF.

L82 ANSWER 13 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-140124 [13] WPIX
DNC C2000-043611
TI A nucleic acid base-bound oligomer - for use as an anti-allergic or

anti-inflammatory agent.
DC B04 D16
PA (SAKA) OTSUKA SEIYAKU KOGYO KK
CYC 1
PI JP 2000004881 A 20000111 (200013)* 12p C12N015-09
ADT JP 2000004881 A JP 1998-174599 19980622
PRAI JP 1998-174599 19980622
IC ICM C12N015-09
ICA A61K031-70; A61K038-00
AB JP2000004881 A UPAB: 20000313
NOVELTY - A nucleic acid base-bound oligomer having a sequence portion of a base complementary to at least partial base sequence of a gene coding human **stem cell factor (SCF)**.
USE - The nucleic acid base-bound oligomer is useful as an anti-allergic agent and anti-inflammatory agent.
ADVANTAGE - The nucleic acid base-bound oligomer is new.
Dwg.1,4,5/5
FS CPI
FA AB; GI
MC CPI: B04-E01; **B04-H16**; **B14-C03**; B14-G02A; D05-H12A; D05-H17A2

L82 ANSWER 14 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-097470 [08] WPIX
DNC C2000-028280
TI Composition containing immune stimulant and inhibitor of agent that adversely affects the immune response, for treating cancers and infections.
DC B04 D16
IN BRYSCH, W; SCHLINGENSIEPEN, K; SCHLINGENSIEPEN, R
PA (BIOG-N) BIOGNOSTIK GES BIOMOLEKULARE DIAGNOSTIK
CYC 86
PI WO 9963975 A2 19991216 (200008)* EN 29p A61K031-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9951549 A 19991230 (200022) A61K031-00
ADT WO 9963975 A2 WO 1999-EP4013 19990610; AU 9951549 A AU 1999-51549 19990610
FDT AU 9951549 A Based on WO 9963975
PRAI EP 1998-113974 19980725; EP 1998-110709 19980610
IC ICM A61K031-00
AB WO 9963975 A UPAB: 20000215
NOVELTY - Composition (A) contains:
(1) at least one inhibitor (I) of less than 100 kDa, of a substance (II) that adversely affects the immune response, and
(2) at least one stimulant (III) that positively affects the immune response.
(II) is transforming growth factor beta (TGFb), vascular endothelial growth factor (VEGF), interleukin (IL)-10 or prostaglandin E2 (PGE2), or their receptors.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for about 150 specified oligonucleotides (ON) (all are given in the specification).
ACTIVITY - Anticancer; anti-inflammatory; anti-asthmatic; anti-diabetic; anti-atherosclerosis; immunomodulatory; anti-infective.
MECHANISM OF ACTION - (I) inhibits synthesis of agents that suppress, downregulate or adversely affect the immune response, while (III) has a stimulatory effect.
USE - (A) is used as an immunostimulant for treatment of neoplasms and infections, particularly hyperproliferation; leukemia; (non-)Hodgkin lymphoma; carcinoma (of esophagus, bronchi, colon-rectum, stomach, intestine, gall bladder or duct, pancreas, anus, breast, ovary, cervix, endometrium, prostate or bladder), liver tumors, malignant melanoma, brain

tumors and sarcomas. Some new oligonucleotides (ON), most of which are (I) directed against TGFb or VEGF, are inhibitors of monocyte chemotactic protein-1 (MCP-1) and are useful (not claimed) as anti-inflammatories for treating e.g. asthma, Crohn's disease, ulcerative colitis, diabetes, glomerulonephritis, acute respiratory distress syndrome and formation of atherosclerotic plaque.

ADVANTAGE - A single inhibitory oligonucleotide may be active agaisnt two, or all three, of TGF beta 1, beta 2 and beta 3. Human glioma cells were incubated in presence of the known oligonucleotide GCTTTCACCAAATTGGAAGC (no concentration stated) for 3 days, then the culture medium analyzed for TGF beta 1 and beta 2 by enzyme-linked immunosorbent assay. The optical density was about 0.3 and 0.08 for beta 1 and beta 2, respectively, compared with 0.44 and 0.27 for cells grown in absence of the oligonucleotide.

Dwg.0/11

FS CPI

FA AB; DCN

MC CPI: B04-B03C; B04-B04C2; B04-F11; B04-G01; B04-H02; B04-H03B; B04-H04A; B04-H04C; B04-H04D; B04-H05; B04-H06F; B04-N04; **B14-C03**; B14-E08; B14-E10C; B14-F07; B14-G03; B14-K01A; B14-S04; D05-H07; D05-H12D1

TECH UPTX: 20000215

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (I) is:
(1) an antisense and/or ribozyme ON, specifically one of 213 sequences (mostly new) (all are given in the specification), or
(2) is a Fab fragment or single-chain antibody.
Most preferably ON are inhibitory for at least two of TGF beta1, beta2 and beta3. (III) is:
(1) a compound that increases synthesis or function of compounds that stimulate, enhance, upregulate an/or positively influence the immune system, particularly granulocyte-macrophage colony stimulating factor; **stem cell factor**, CSF (not defined), interferon, Flt-3 ligand, monocyte chemotactic protein-1 (MCP-1), or ILs 2, 4, 12 and/or 18;
(2) one of these ILs; or
(3) is a virus; an antigen (of viral, pathogen or tumor origin); organ-specific antigen expressed in an affected organ that is not essential for the organism, or a fusion of dendritic and tumor cells.
Optionally (A) includes two or more of (I) and/or (III).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: ON are made by usual methods of chemical synthesis, and they may incorporate standard modifications to bases, sugars and/or intersugar links. Optionally ON may be conjugated to e.g. folic acid, steroid hormones, peptides etc.

L82 ANSWER 15 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 2000-086568 [07] WPIX

DNC C2000-024060

TI Sustained-release alginate gel composition for treating e.g. excess weight, diabetes and stroke.

DC A96 B04 B07

IN GOLDENBERG, M S; GU, J H

PA (AMGE-N) AMGEN INC

CYC 85

PI WO 9959549 A1 19991125 (200007)* EN 50p A61K009-16
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 9939939 A 19991206 (200019) A61K009-16

ADT WO 9959549 A1 WO 1999-US10737 19990514; AU 9939939 A AU 1999-39939 19990514

FDT AU 9939939 A Based on WO 9959549

PRAI US 1998-80832 19980518

IC ICM A61K009-16
ICS A61K047-36

AB WO 9959549 A UPAB: 20000209
NOVELTY - Sustained release delayed gel composition comprises a hydrophilic polymer, a biologically active agent and at least one bound polyvalent metal ion in which the gel is biodegradable.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for production of a sustained release composition which comprises:
(1) dissolving a biologically active agent and a hydrophilic polymer with a solvent to form a first mixture;
(2) dissolving at least one precipitating agent in a solvent to form a second mixture;
(3) adding the first mixture with the second mixture and
(4) co-precipitating the active agent with the hydrophilic polymer to form a biodegradable gel particle.
ACTIVITY - Sustained-Release; Antidiabetic; Antiarteriosclerotic; Litholytic; Hepatotropic; Cerebroprotective.
To a solution of 2.39% ethyl ester alginate (30 mol.%), is added 0.1M acetate buffer (pH 4.5, 100 mu l), GCSF (1-4 mu l) and distilled water (246 ml). The mixture is stirred well. A suspension of 1M CaHPO4 (10 mu l) and a solution of 1.68M delta -gluconolactone (40 mu l) are thoroughly stirred into this mixture. The final mixture (0.2 ml) is cast and left overnight at 4 deg. C to gel. After overnight storage in vitro release is conducted in 10 mM Tris buffer, pH 7.5. This cast ethyl ester alginate gel with 30 mol.% degree of esterification exhibits less than 5% burst and sustained release showing 20% release in 1 day and 40% release in 2 days.
USE - The composition can be used for treating disorders such as excess weight, diabetes, high blood lipid level, arteriosclerosis, arterial plaque, insufficient lean tissue mass, insufficient sensitivity to insulin, stroke and for the reduction or prevention of gall stones formation. The composition can also be used for treating hematopoietic cell deficiencies, infection and neutropenia. The composition is useful for preventing or inhibiting the formation of tissue adhesions following surgery and traumatic injury, for supplementing tissues, to fill a confined space with a resorbable material, as a scaffold for tissue growth and as a wound dressing.
ADVANTAGE - The composition provides a method for improving the bioavailability of the active agent and for obtaining a constant blood level over time.
Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: A03-A00A; A09-A07; A10-E07; A12-S; A12-V01; A12-V03A; B04-C02D; B04-H02B; B04-H04; B04-H05; B04-H06; B04-H07; B04-H08; **B04-H16**; B04-N02; B05-A02; B05-A03; B12-M03; B12-M10A; B12-M10B; B12-M11D; **B14-C03**; B14-E11; B14-E12; B14-F03; B14-F06; B14-F07; B14-F09

TECH UPTX: 20000209
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The bound polyvalent metal ion comprises a mixture of bound and unbound polyvalent metal ion. The gel also comprises excipients for stabilizing the biologically active agent or the hydrophilic polymer. The bound polyvalent metal ion comprises a salt comprising acetates, phosphates, lactates, tartrates, citrates, chlorides, carbonates or hydroxides. The metal ion comprises manganese, strontium, iron, magnesium, calcium, barium, copper, aluminium or zinc.
The proton donor is from an acid source, preferably buffers, esters, slowly dissolving acids or lactones. The hydrophilic polymer is a polyanion or a polysaccharide, preferably an acidic polysaccharide, especially an alginate. The alginate contains at least 30% guluronic acid. The biologically active agent comprises a protein and the composition has improved bioavailability. The protein is a hematopoietic factor, colony stimulating factor, anti-obesity factor, growth factor, trophic factor or antiinflammatory factor. Alternatively the protein is leptin, G-CSF, **SCF**, BDNF, GDNF, NT3, GM-CSF, IL-Ira, IL2, TNF-bp, MGDF, OPG, interferons, erythropoietin, KGF, insulin or their analogues or

derivatives.
The biologically active agent is a complexed biologically active agent which is preferably a precipitated protein. The precipitated protein is preferably a zinc leptin precipitate.
Preferred Method: The method also comprises mixing with the second mixture at least one proton donor capable of releasing the bound polyvalent metal ion. The first mixture is concentrated before mixing the proton donor or bound polyvalent metal ion. The method provides a constant blood level of the biologically active agent over time in the patient. The acid source is delta-gluconolactone.

L82 ANSWER 16 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-601764 [51] WPIX
DNC C1999-175202
TI Inhibitors and stimulators of stem cell proliferation for treating e.g. autoimmune diseases, cancer, psoriasis, AIDS, anemia or pain.
DC B04 D16 D22
IN TSYRLOVA, I; WOLPE, S D
PA (PRON-N) PRO-NEURON INC
CYC 1
PI ZA 9802746 A 19990526 (199951)* 153p C12N000-00
ADT ZA 9802746 A ZA 1998-2746 19980401
PRAI US 1997-832443 19970403
IC ICM C12N000-00
ICS A61K000-00
AB ZA 9802746 A UPAB: 19991207
NOVELTY - New polypeptide comprising an alpha hemoglobin chain (AHC) with a substituted or deleted C-terminal hydrophobic domain is an inhibitor of stem cell proliferation (INPROL).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
(1) a polypeptide comprising an AHC with the C-terminal haptoglobin-binding domain substituted or deleted;
(2) a polypeptide comprising amino acids 1-97 of human AHC;
(3) a composition comprising polypeptides of (1), (2) or (3) with a carrier;
(4) a method for expressing alpha hemoglobin or it's substitution or deletion analogs as a ubiquitin fusion protein;
(5) a peptide with sequence (I), (II), (III) or (IV);
(6) a method of stimulating stem cell proliferation comprising contacting hematopoeitic cells (HCs) with INPROL and/or an opiate compound capable of binding opiate receptors;
(7) a method of stimulating or inhibiting stem cell proliferation comprising contacting HCs with a compound capable of binding nociceptin receptors or a compound capable of activating the G inhibitory subclass of GTP binding proteins;
(8) a method of conducting gene therapy in a mammal comprising:
(a) removing HCs from the mammal and treating them ex vivo with a stem cell stimulatory amount of INPROL and/or opiate compound;
(b) transfecting or infecting the HCs with a predetermined gene;
(c) contacting the transfected HCs ex vivo with a stem cell inhibitory amount of INPROL and/or an opiate compound;
(d) transplanting the HCs back into the mammal; and
(e) optionally treating the mammal in vivo with a stem cell inhibitory or stimulatory quantity of INPROL and/or an opiate compound;
(9) a composition comprising an opiate compound and at least one inhibitory compound selected from MIP-1 alpha , TGF beta , TNF alpha , INF alpha , INF beta , INF gamma , the pentapeptide pyroGlu-Glu-Asp-Cys-Lys, the tetrapeptide M-acetyl-Ser-Asp-Lys-Pro, and the tripeptide glutathione (Gly-Cys- gamma Glu); and
(10) a composition comprising an opiate compound and at least one stimulatory compound selected from IL-1 to IL-15, G-CSF, GM-CSF, M-CSF, erythropoietin, thrombopoietin, **stem cell factor** and flk2/flt3 ligand.
ACTIVITY - Anti-HIV; immunosuppressive; cytostatic; neuroprotective; antipsoriatic; antianemic; analgesic.
MECHANISM OF ACTION - Inhibitor and/or stimulator of stem cell

proliferation.

USE - The polypeptides and compositions can be used for modulating stem cell proliferation (claimed) to regulate the stem cell cycle for the treatment of humans or animals with autoimmune diseases, cancer, myelodysplasia, preleukemia, leukemia, psoriasis, AIDS, myelodysplastic syndromes, aplastic anemia or other diseases involving hyper- or hypo-proliferative conditions, and also for inducing analgesia. The compositions provide a method of treating humans or animals anticipating or having undergone exposure to chemotherapeutic agents or agents which damage cycling stem cells, radiation exposure and provide protection against these agents during ex vivo treatments. They also relate to the improvement of stem cell maintenance or expansion cultures for auto- and allo-transplantation procedures or for gene transfer, as well as for in vivo treatments to improve such procedures (claimed). The cancer treatment comprises removing hematopoietic cells from a mammal, treating the cells ex vivo with a preparation comprising a modified AHC, treating the cells with chemotherapy or radiation, performing myeloblative treatment on the mammal and transplanting the treated hematopoietic cells back into the mammal (claimed). The hematopoietic cells used are bone marrow cells, peripheral blood cells, mobilized peripheral blood cells, fetal liver or umbilical cord blood cells.

Once a mammal has been treated with radiotherapy and/or chemotherapy which damages or destroys stem cells the INPROL and/or an opiate compound is administered to stimulate stem cell division and to treat or prevent stem cell exhaustion.

The polypeptides can be used to identify a receptor for INPROL by contacting a material thought to contain the receptor with INPROL in a receptor-binding assay which is preferably an adenylate cyclase assay (claimed).

ADVANTAGE - The compositions differentially protect normal stem cells in a mammal from chemotherapy or radiation.

Dwg.0/23

FS CPI

FA AB; DCN

MC CPI: B04-C01C; B04-C01G; B04-E03F; B04-E08; B04-F02; B04-F0200E; B04-N02A; B11-C08D; B14-C01; B14-F03; B14-G01B; B14-G02D; B14-H01A; B14-J01; B14-L01; B14-L06; **B14-N17C**; B14-S03; D05-H09; D05-H12A; D05-H12E; D05-H14B2; D09-A

TECH UPTX: 19991207

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Opiate: The opiate compound may be morphine, etorphine, codiene, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, hydrocodone, oxycodone, nalorphine, naloxone, naltrexone, buprenorphin, butanorphanol, nalbuphine, meperidine, alphaprodine, diphenoxylate, fentanyl, DAMGO (a derivative of enkephalins), DALDA (a derivative of dermorphin) or nociceptin.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: Polypeptides corresponding to AHC sequences were expressed as ubiquitin fusion proteins using Escherichia coli.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Polypeptide: The C-terminal hydrophobic domain of human alpha hemoglobin is comprised of amino acids 98-141 and its removal or modification improves the solubility of the polypeptide. The haptoglobin binding domain of human alpha hemoglobin is comprised of amino acids 121-127 and its removal or modification improves the pharmacokinetic properties of the polypeptide.
Preferred Inhibitor: The INPROL may be the alpha chain of hemoglobin, the beta chain of hemoglobin, the gamma chain of hemoglobin, the delta chain of hemoglobin, the epsilon chain of hemoglobin, the zeta chain of hemoglobin, a polypeptide having the sequence of amino acids 1-97 of the human alpha hemoglobin chain, a polypeptide having the sequence of amino acids 1-94 of the human alpha hemoglobin chain, peptides (I)-(IV) or peptides such as Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val, Cys-Phe-Pro-His-Phe-Asp-Leu-Ser-His-Gly-Ser-Ala-Gln-Val-Cys (where the two Cys residues form a disulfide bond), Leu-Val-Val-Tyr-Pro or Tyr-Pro-Trp-Thr.

Preferred Receptor: The opiate-like receptor includes the classical mu, kappa or delta opiate receptors of ORL1.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compositions: The composition comprises 0.1 mg - 6g of the polypeptides, a polypeptide comprising amino acids 1-97 of human AHC and/or a polypeptide comprising amino acids 1-94 of human AHC.

L82 ANSWER 17 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-404890 [34] WPIX
DNC C1999-119443
TI Altering cytokine activity in an animal cell.
DC B04
IN BONAVIDA, B; GAN, X
PA (REGC) UNIV CALIFORNIA
CYC 82
PI WO 9929329 A1 19990617 (199934)* EN 66p A61K033-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9918051 A 19990628 (199946) A61K033-00
ADT WO 9929329 A1 WO 1998-US25807 19981204; AU 9918051 A AU 1999-18051 19981204
FDT AU 9918051 A Based on WO 9929329
PRAI US 1997-67676 19971205
IC ICM A61K033-00
ICS A61K035-08
AB WO 9929329 A UPAB: 19990825
NOVELTY - Altering cytokine activity in an animal cell by providing to the cell an amount of an IE water composition is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included the following:
(1) increasing the concentration of a cytokine in an animal cell, comprising providing to the cell an amount of an IE water composition;
(2) increasing the amount of a cytokine secreted from an animal cell, comprising contacting the cell with an IE water composition;
(3) increasing the rate of secretion of a cytokine from an animal cell, comprising contacting said cell with an IE water composition;
(4) stimulating a mammalian blood cell to produce a cytokine, comprising contacting said cell with an amount of an IE water composition;
(5) producing an immune response in an animal, comprising administering to the animal an amount of an IE water composition effective to produce the response in the animal;
(6) inducing differentiation in an animal cell, comprising administering to the cell an amount of an IE water composition;
(7) treating an autoimmune disease in an animal, comprising administering an IE water composition;
(8) treating cancer in an animal by administering an IE water composition; and
(9) a kit comprising containers comprising IE water composition.
USE - The method is used to treat autoimmune disease is selected from psoriasis, lupus, Sjogren's syndrome, rheumatoid arthritis, ulcerative colitis, Crohn's disease, sympathetic ophthalmia, myasthenia gravis, multiple sclerosis, orchitis and osteomyelitis, or cancer is selected from leukemia, sarcoma, melanoma, glioblastoma, prostate cancer, ovarian cancer, lung cancer, and colon cancer (all claimed). Chemokines are molecules involved in attracting various types of immune cells to sites of action. MCP-1 (monocyte chemotactic protein-1), MIP-1 alpha (macrophage inflammatory protein- I alpha), and RANTES (regulated upon activation, normal T cells expressed and secreted). These chemokines are chemotactic for monocytes, lymphocytes, dendritic cells, eosinophils, and basophils. They are secreted by various types of cells involved in the regulation of THI and TH2 types of immune responses. IE water triggers cytokine

secretion by PBMC, where it also affects the secretion of other family mediators involved in cell-cell sites. The chemokines are significantly induced by IE water, over 50 fold background levels with laboratory control water. In the tests carried the stimulation was comparable to the most potent activation of chemokine products by LPS. These findings emphasize the role of IE water in the positive regulation of host immune defense mechanisms.

ADVANTAGE - None given.

Dwg.0/10

FS CPI

FA AB; DCN

MC CPI: B05-C08; B14-C09B; B14-D01B; B14-G02D; B14-G03; B14-H01; B14-J05; B14-N03; **B14-N17**; B14-S01

TECH UPTX: 19990825

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Materials: The animal cell is a mammalian (especially a human) cell selected from a bone marrow cell, a pluripotent stem cell, a blood progenitor cell, a blood cell, a brain cell, an aging cell, a cancer cell and a tumor cell, especially a peripheral blood monocyte. The cytokine is selected from the group consisting of interferon (IFN)-gamma, interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, tumor necrosis factor (TNF)-alpha, TNF-beta, IL-15, IL-18, GM-CSF, CSF, **SCF**, Fas-R, Fas-L, TRAIL, and TRAIL receptor. The composition further comprises an immuno-modulating agent selected from a mitogen, a cytokine, an antigen, a chemotherapeutic agent, a polypeptide, a polynucleotide, and an antibody. The cell is comprised with an animal and the cell is contacted with the composition by administering the composition to the animal, orally, subcutaneously, intramuscularly or intravenously. The IE water composition further comprises a polynucleotide or a polypeptide. In method (8), the composition further comprises an anticancer agent, selected from the group consisting of cisplatin, adriamycin, doxorubicin, etoposide, camptothecin, actinomycin D, cyclophosphamide, and 5-fluorouracil.

Preferred Method: The method (7) further comprising administering to the animal an immuno-modulator or an immuno-suppressant.

Preferred Kit: The kit comprises an excipient, an immuno-modulating agent, an immunosuppressive agent, a cytokine, an anticancer agent, a polynucleotide, a polypeptide, a carbohydrate, or a lipid.

L82 ANSWER 18 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1999-385175 [32] WPIX

DNC C1999-113221

TI New cellular composition comprising mammalian peripheral blood mononuclear cells useful for transplantation.

DC B04

IN ILDSTAD, S T; ZORINA, T D

PA (ILDS-I) ILDSTAD S T; (UYAL-N) UNIV ALLEGHENY HEALTH SCI; (ZORI-I) ZORINA T D

CYC 82

PI WO 9926639 A1 19990603 (199932)* EN 69p A61K035-12

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 9917055 A 19990615 (199944) A61K035-12

ADT WO 9926639 A1 WO 1998-US25368 19981124; AU 9917055 A AU 1999-17055 19981124

FDT AU 9917055 A Based on WO 9926639

PRAI US 1998-72862 19980505; US 1997-66821 19971126; US 1997-986511 19971208

IC ICM A61K035-12

ICS A61K035-28; A61K038-18; A61K038-19; A61K038-20; C12N005-00

AB WO 9926639 A UPAB: 19990813

NOVELTY - A cellular composition comprising mammalian peripheral blood mononuclear cells enriched in hematopoietic stem cells and facilitating

cells, and depleted of graft versus-host disease producing cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a cellular composition comprising human peripheral blood mononuclear cells enriched in hematopoietic stem cells (HSC) and facilitating cells (FC);

(2) a method for preparing mammalian/human peripheral blood mononuclear cells enriched in HSC and FC comprising;

(3) a method for reconstituting bone marrow in a human recipient comprising administering the pharmaceutical composition comprising the cellular composition into the recipient; and

(4) a method for preparing mammalian/human hematopoietic cells (HC) enriched in HSC and FC comprising treating a mammalian/human cell population with a composition that activates the granulocyte-macrophage colony stimulating factor (GM-CSF) receptor and the tumor necrosis factor (TNF) receptor so that the HSC and FC are increased in number.

ACTIVITY - Immunosuppressive; anticancer; antianemic; antiarthrytic.

MECHANISM OF ACTION - The donor's blood contains both mobilized facilitating cells and hematopoietic stem cells, and can be used to repopulate the destroyed lymphohematopoietic system of a patient.

USE - The composition is useful in a pharmaceutical composition for reconstitution of bone marrow of a recipient in which the hematopoietic stem cells and facilitating cells are histocompatible with the recipient (claimed). The composition is useful as a source of donor cells in bone marrow transplantation (especially as a form of gene therapy) for treating a variety of disorders e.g. cancer, anemia, autoimmunity (e.g. type I diabetes, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, psoriasis, colitis and even Alzheimer's disease), immunodeficiency and even viral infections. Alternatively the donor's hematopoetic tissue e.g. bone marrow can be ex vivo treated to enrich selectively for FC and HSC populations by activating appropriate cell surface receptors.

ADVANTAGE - Bone marrow transplantation is an effective form of treatment of hematologic tumors and anemias. Mobilization of HSC and FC into the peripheral blood of the subject stimulates FLK2/FLT3 and G-CSF receptor to produce high yields of HSC and FC. Also non-human HSC and FC may be used to enhance engraftment of xenogenic cells in human patients without any side effects and induces donor-specific tolerance to allow permanent acceptance of donor's cells, tissues and organs.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B04-F01; B14-A02; B14-C09B; B14-E10C; B14-F03; B14-G02D; B14-H01; B14-J01A4; **B14-N17C**; B14-S01

TECH UPTX: 19990813

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: The cellular composition of the human peripheral blood mononuclear cells further comprises depletion of the graft-versus-host disease producing cells. The mammalian cell composition is enriched in CD34+ and CD8+ cells, and is depleted of alpha betaTCR+ and gamma deltaTCR+ cells.

Preferred Method: The method (4) further comprises treating the cell population with a composition that activates FLT3, the **SCF** receptor, the granulocyte-colony stimulating factor (G-CSF) receptor, the interleukin (IL)-7 receptor and/or the IL-12 receptor.

Preparation: Preparation of human/mammalian peripheral blood mononuclear cells comprises:

(a) treating a donor with a composition that activates FLT3 and the G-CSF, so that the HSC and FC are mobilized (especially by treating the donor with G-CSF and FLT-3 ligand) into the circulation;

(b) collecting the peripheral blood mononuclear cells (especially at least 8 days subsequent to initial treatment) from the donor when both HSC and FC are mobilized; and

(c) further (if preparing mammalian peripheral blood mononuclear cells) depleting the collected peripheral blood mononuclear cells of graft-versus-host disease producing cells.

L82 ANSWER 19 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-357170 [30] WPIX
DNC C1999-105554
TI Treating asthma and eosinophilia.
DC B04 D13 D16
IN BROWNELL, E; KUNKEL, S L; LUKACS, N; STRIETER, R M
PA (FARB) BAYER CORP; (UNMI) UNIV MICHIGAN
CYC 1
PI US 5911988 A 19990615 (199930)* 21p A61K039-395
ADT US 5911988 A Cont of US 1995-431314 19950428, US 1997-912541 19970818
PRAI US 1995-431314 19950428; US 1997-912541 19970818
IC ICM A61K039-395
AB US 5911988 A UPAB: 19990802
NOVELTY - A method (I) for treating asthma and inhibiting eosinophilia in the lungs of mammals by disrupting interaction between **Stem Cell Factor** (**SCF**) and **SCF**-receptor proteins using anti-**SCF** antibodies, is new.
DETAILED DESCRIPTION - A method (I) for inhibiting eosinophil infiltration into a mammal's lung by inhibiting the interaction between **SCF** and **SCF**-receptor proteins. (I) comprises contacting lung tissue (by intra-tracheal administration) with an antibody (or antigen binding fragment) that specifically binds **SCF**, therefore inhibiting the interaction between **SCF** and **SCF**-receptor proteins so that antigen stimulated eosinophil infiltration to the lung is inhibited.
USE - (I) may be used to treat asthma (and associated inflammation) and inhibit antigen stimulated eosinophil infiltration of lung tissue.
DESCRIPTION OF DRAWING(S) - The graph shows the effect of anti-**SCF** antibodies administered with intra-tracheal SEA, as expressed as a percentage of eosinophils compared to total BAL leukocytes (the cells were washed out from the airway by bronchial alveolar lavage (BAL)).
Dwg.0/10
FS CPI
FA AB; DCN
MC CPI: B04-G02; **B14-C03**; B14-K01A; D05-H07; D05-H09; D05-H11A; D05-H11B
TECH UPTX: 19990802
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Antibody: In (I), the antibody used may be either polyclonal or monclonal.

L82 ANSWER 20 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-246902 [21] WPIX
DNC C1999-072290
TI Topical compositions containing hypophysis extract for the repair or regeneration of melanocytes.
DC B04 D21
IN GAUTHIER, Y; PODESTA, M H; TASSI LE MOULT, C; TRASSARD, C; VIORNERY, P
PA (GAUT-I) GAUTHIER Y; (PODE-I) PODESTA M H; (LMOU-I) TASSI LE MOULT C; (TRAS-I) TRASSARD C; (VIOR-I) VIORNERY P
CYC 1
PI FR 2769225 A1 19990409 (199921)* 9p A61K035-55
ADT FR 2769225 A1 FR 1997-12342 19971003
PRAI FR 1997-12342 19971003
IC ICM A61K035-55
ICS A61K007-48
AB FR 2769225 A UPAB: 19990603
NOVELTY - Use of hypophysis extracts in compositions for promoting pigmentation.
DETAILED DESCRIPTION - Topical composition for the repair or regeneration of melanocytes comprises hypophysis extracts and a carrier.
MECHANISM OF ACTION - Melanin-concentrating hormone.
USE - The composition is used in the treatment of skin depigmentation related to post-therapeutic scars, achromic scars and secondary achromia or achromia due to vitiligo.
ADVANTAGE - The desired therapeutic effect is achieved in 20 - 40 days.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-H06; **B14-N17**; D08-B09A
TECH UPTX: 19990603
TECHNOLOGY FOCUS - PHARMACEUTICALS - The composition may contain growth factors selected from endothelin, bFGF2 and **SCF**, as well as mineral salts, natural or synthetic amino acids and vitamin factors. The extract is used in amount of 1-100 mg per 100g of composition or in graded doses of 1-200 microg per ml of composition. The excipient is preferably solid or semi-viscous, preferably in the form of a fluid or powdered vehicle.

L82 ANSWER 21 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-229239 [19] WPIX
DNN N1999-169623 DNC C1999-067440
TI Rin2 polypeptides and related nucleic acid.
DC B04 D16 S03
IN GALLI, S J; TAM, S; TSAI, M
PA (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT
CYC 22
PI WO 9913079 A1 19990318 (199919)* EN 101p C12N015-12
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9893156 A 19990329 (199932) C12N015-12
US 5965707 A 19991012 (199949) A61K038-16
ADT WO 9913079 A1 WO 1998-US19056 19980911; AU 9893156 A AU 1998-93156 19980911; US 5965707 A Provisional US 1997-58520 19970911, US 1997-942819 19971002
FDT AU 9893156 A Based on WO 9913079
PRAI US 1997-942819 19971002; US 1997-58520 19970911
IC ICM A61K038-16; C12N015-12
ICS C07K001-00; C07K014-47; C07K016-18; C12Q001-68; G01N033-50; G01N033-53
AB WO 9913079 A UPAB: 19990518
NOVELTY - Isolated Rin2 polypeptides (I) which downregulate functional responses elicited by Ras-dependent signaling pathways, and their active derivatives and fragments.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) isolated nucleic acid (II) that encodes (I);
(2) DNA constructs containing (II) plus regulatory sequences;
(3) recombinant host cells containing this construct;
(4) production of recombinant (I) by culturing these cells;
(5) antibody, or its antigen-binding fragments, that binds specifically to (I);
(6) method for identifying agents (A) that alter activity of (I); and
(7) (A) identified this way.
ACTIVITY - anti-allergic; antiproliferative; anticancer; antidiabetic; anti-arthritic; anti-inflammatory; angiogenic; cell-proliferative.
MECHANISM OF ACTION - Ras-dependent signaling is involved in release of mediators from mast cells; T cell function, and cell proliferation. (A) modulate this signaling (or functional responses dependent on it) in cells that express an appropriate receptor, particularly a Fc epsilon RI, TrkA (for nerve growth factor), **c-kit** or T cell receptor, with functional responses being:
(1) activation of Erk-MAP, JNK or p39 MAP kinases;
(2) cellular secretion (particularly of preformed or lipid mediators and/or cytokines). cDNA encoding murine Rin2 was cloned, in antisense orientation, into pBK-CMV and the plasmid used to transform C1.MC/C57.1 murine mast cells.
When the Fc epsilon RI receptor was activated (crosslinked) in the transformed cells, activation of Erk-MAP kinase was strongly potentiated (after 30 min, about double the activity of cells transformed with empty pBK-CMV). JNK and p39 MAP kinase were also potentiated.

USE - Agents that increase Rin2 activity (particularly Rin2 itself, optionally expressed from a vector) are used to treat allergy (asthma, hayfever or atopic eczema); Ras-dependent cancers and (non-)neoplastic cellular proliferation; autoimmune diseases; T cell-associated diseases and T cell dependent graft vs. host disease (typical examples being type I diabetes mellitus; multiple sclerosis, Crohn's disease, autoimmune hepatitis and psoriasis).

Agents that inhibit Rin2 activity are used to improve wound healing; angiogenesis and/or re-epithelialization (also to improve immune response to pathogens; in human immune deficiency virus, and some other, infections; immune suppression associated with cancer therapy, and nerve regeneration).

(I) is useful as molecular weight marker, to raise specific antibodies and therapeutically.

(II) is used to express recombinant (I); as antisense molecules for reducing Rin2 expression; to identify Rin2 gene mutations and to identify proteins that bind specifically to Rin2 (in two-hybrid assays). Antibodies specific for (I) are used to detect (I) in cells or lysates by standard immunoassays, also as Rin2 inhibitors and reagents for studying Ras-effector pathways.

Dwg.0/15

FS CPI EPI

FA AB; DCN

MC CPI: B04-E03F; B04-E08; B04-F0100E; B04-G0100E; B04-N02A; B11-C07; B12-K04A; B14-A02B1; **B14-C03**; B14-C09; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-H01B; B14-K01A; B14-N12; **B14-N17**; B14-S01; B14-S04; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12D2; D05-H12D4; D05-H12E; D05-H14; D05-H17A6; D05-H18B

EPI: S03-E14H; S03-E14H4

TECH UPTX: 19990510

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred polypeptides: (I) particularly down regulates FcepsilonRI aggregation and has a 491 amino acid (aa) sequence (Ia) given in the specification, or is at least 40% similar to (Ia). Preferred nucleic acid: (II) is a 2664 bp sequence (IIa), encoding (Ia), or its fragment or derivative, particularly a fragment extending from nucleotides 51-405; 532-1276; 885-1144 or containing the 822 3'-terminal bp of (IIa), or their complements, derivatives or fragments. (I) may also be any sequence with at least 75, preferably 90,% identity with (IIa) or the specified fragments.

Preferred assay: To identify (A), a cell containing (I) is subjected to a stimulus that activates at least one Ras-dependent pathway in the cell, in presence and absence of test compound, and any alteration of (I) activity detected. The stimulus is particularly nerve growth factor, **stem cell factor**; peptide antigen and major histocompatibility molecules, or immunoglobulin E (IgE) plus specific antigen. Typical compounds for testing are Rin2 derivatives or mimics.

Preparation: (I) can be isolated from natural sources and antibodies are produced by usual immunization or cell fusion techniques.

Cells of the growth factor-independent murine mast cell line C1.MC/C57.1 were sensitized to anti-DNP (dinitrophenyl) IgE, then challenged with hapten and total RNA extracted at various times from both stimulated and unstimulated cells. Conventional differential display analysis was performed to identify a clone (60-4, 382 bp) that was expressed in activated cells. This was used as probe to screen a mouse mast cell cDNA library to identify clone SY-6 containing a 1.1 kb insert. This was used to screen a mouse brain library to isolate a clone, SY-A, containing sequence (Ia). Once identified this sequence may be expressed in standard vector/host cell systems, in sense or antisense orientations, e.g. for expression of Rin2 polypeptides, optionally as fusion proteins. The sequences was also used to isolate the corresponding human cDNA.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) can be synthesized by standard chemical methods.

L82 ANSWER 22 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1997-512718 [47] WPIX

DNC C1997-163717
TI **Stem cell factor** analogue N10D or N10D/N11D
- useful to treat pigmentation disorder, AIDS, nerve damage, infertility, intestinal damage or haematopoietic disorder.
DC B04 D16
IN LU, H S; LU, H
PA (AMGE-N) AMGEN INC; (AMGE-N) AMGEN BOULDER INC
CYC 77
PI WO 9738101 A1 19971016 (199747)* EN 42p C12N015-12
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9726064 A 19971029 (199810) C12N015-12
NO 9804491 A 19981005 (199901) C07K014-475
CZ 9803015 A3 19990113 (199908) C12N015-12
EP 904367 A1 19990331 (199917) EN C12N015-12
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI
SK 9801310 A3 19990312 (199919) C12N015-12
US 5885962 A 19990323 (199919) A61K038-18
CN 1214734 A 19990421 (199934) C12N015-12
BR 9708578 A 19990803 (199952) C12N015-12
HU 9902768 A2 20000128 (200015) C12N015-12
JP 2000508170 W 20000704 (200037) 38p C12N015-09
MX 9807807 A1 19990201 (200055) C12N015-12
KR 2000004951 A 20000125 (200061) C12N015-12
AU 726663 B 20001116 (200103) C12N015-12
ADT WO 9738101 A1 WO 1997-US5541 19970403; AU 9726064 A AU 1997-26064 19970403; NO 9804491 A WO 1997-US5541 19970403, NO 1998-4491 19980925; CZ 9803015 A3 WO 1997-US5541 19970403, CZ 1998-3015 19970403; EP 904367 A1 EP 1997-917841 19970403, WO 1997-US5541 19970403; SK 9801310 A3 WO 1997-US5541 19970403, SK 1998-1310 19970403; US 5885962 A US 1996-628428 19960405; CN 1214734 A CN 1997-193342 19970403; BR 9708578 A BR 1997-8578 19970403, WO 1997-US5541 19970403; HU 9902768 A2 WO 1997-US5541 19970403, HU 1999-2768 19970403; JP 2000508170 W JP 1997-536320 19970403, WO 1997-US5541 19970403; MX 9807807 A1 MX 1998-7807 19980924; KR 2000004951 A WO 1997-US5541 19970403, KR 1998-707544 19980923; AU 726663 B AU 1997-26064 19970403
FDT AU 9726064 A Based on WO 9738101; CZ 9803015 A3 Based on WO 9738101; EP 904367 A1 Based on WO 9738101; BR 9708578 A Based on WO 9738101; HU 9902768 A2 Based on WO 9738101; JP 2000508170 W Based on WO 9738101; KR 2000004951 A Based on WO 9738101; AU 726663 B Previous Publ. AU 9726064, Based on WO 9738101
PRAI US 1996-628428 19960405
REP 3.Jnl.Ref; EP 676470; GB 2258234; WO 9105795; WO 9200376; WO 9203459
IC ICM A61K038-18; C07K014-475; C12N015-09; C12N015-12
ICS A61K038-00; A61K038-22; A61P007-00; A61P007-06; A61P037-04; C07K014-46; C12N001-15; C12N001-19; C12N001-21; C12N005-08; C12N005-10
AB WO 9738101 A UPAB: 20001209
Stem cell factor (**SCF**) analogue Asn10Asp (N10D) or Asn10Asp/Asn11Asp (N10D/N11D) in a diluent, adjuvant or carrier, is claimed. Also claimed are: (1) DNA molecule encoding the **SCF** analogue; (2) DNA viral or plasmid vector containing the DNA molecule; and (3) host cell containing the DNA molecule.

USE - The **SCF** analogue, which has an increased biological activity and stability compared to unmodified **SCF**, can be used treat pigmentation disorders, e.g. vitilago, acquired immunodeficiency syndrome, nerve damage, infertility, intestinal damage or a haematopoietic disorder, e.g. peucopaeneia, thrombocytopaenia or anaemia, enhance bone marrow engraftment during transplantation or bone marrow recovery following radiation, chemical or chemotherapeutic induced bone marrow aplasia or myelosuppression, sensitise cells to chemotherapy or mobilise peripheral blood progenitor cells. It can also be used in an in vitro

haematopoietic cell, preferably bone marrow or peripheral blood progenitor cell, culture medium, where the cells are optionally subsequently transfected with exogenous DNA.
Dwg.0/2
FS CPI
FA AB
MC CPI: B04-E03; B04-E08; B04-F01; **B04-H16**; B11-C09; B14-F03; B14-G01B; B14-G02C; **B14-N17**; B14-P02; D05-H01; D05-H08; D05-H12B2; D05-H12E; D05-H14; D05-H17B2

L82 ANSWER 23 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1997-145689 [13] WPIX
DNC C1997-046600
TI New isolated feline **stem cell factor** DNA - used to develop prods. for the diagnosis, therapy and prophylaxis of feline disorders e.g. parasitic or bacterial infections, allergies, etc.
DC B04 C06 D16
IN DUNHAM, S P; LEES, G M; ONIONS, D E
PA (QONE-N) Q-ONE BIOTECH LTD
CYC 21
PI WO 9705251 A2 19970213 (199713)* EN 29p C12N015-12
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9667457 A 19970226 (199725) C12N015-12
WO 9705251 A3 19970417 (199731) C12N015-12
ADT WO 9705251 A2 WO 1996-GB1904 19960802; AU 9667457 A AU 1996-67457 19960802; WO 9705251 A3 WO 1996-GB1904 19960802
FDT AU 9667457 A Based on WO 9705251
PRAI GB 1995-15839 19950802
REP 1.Jnl.Ref; WO 9105795; WO 9200376; WO 9203459; WO 9409803; WO 9517206
IC ICM C12N015-12
ICS C07K014-475; C12N005-10
AB WO 9705251 A UPAB: 19970326
A polynucleotide fragment (PF) encoding a feline **stem cell factor** (**SCF**) is new.
USE - The prods. can be used to develop agents for the diagnosis, therapy and prophylaxis of feline disorders such as cancer, endotoxaemia, parasitic and bacterial infections, wound therapy, autoimmune and inflammatory diseases and allergies. The feline **SCF** can be used in the treatment of anaemia, leukopaenia, immunosuppression associated with retroviral or non-retroviral agents, chronic infections of bacterial, viral or parasitic origin, and hypo-pigmentation and other skin disorders and for the manipulation of fertility.
Dwg.0/4
FS CPI
FA AB
MC CPI: B04-E01; C04-E01; B04-E02; C04-E02; B12-K04A; C12-K04A; B14-A01; C14-A01; B14-A02; C14-A02; B14-B02; C14-B02; **B14-C03**; **C14-C03**; B14-F03; C14-F03; B14-G02A; C14-G02A; B14-G02D; C14-G02D; B14-H01; C14-H01; **B14-N17**; **C14-N17**; B14-N17B; C14-N17B; D05-H11; D05-H12A; D05-H14; D05-H17A2

L82 ANSWER 24 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1997-087173 [08] WPIX
DNC C1997-028330
TI Use of hepatocyte growth factor antagonists - for inducing apoptosis in cells, partic. for treating myeloid leukaemia or enriching uncommitted progenitor cells.
DC B04 D16
IN BASTIRAS, S; CHEAH, K; LOPEZ, A F; ROBINS, A; SENN, C R; SHANNON, M F; VADAS, M A
PA (BRES-N) BRESAGEN LTD; (MEDV-N) MEDVET SCI PTY LTD
CYC 72
PI WO 9700695 A1 19970109 (199708)* EN 48p A61K038-18
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN

AU 9661153 A 19970122 (199719) A61K038-18
EP 871470 A1 19981021 (199846) EN A61K038-18
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT SE SI
AU 703052 B 19990311 (199922) A61K038-18
JP 11507927 W 19990713 (199938) 64p A61K038-22
AU 9934974 A 19990909 (199949)# A61K038-18
NZ 310366 A 19991129 (200031) A61K038-18

ADT WO 9700695 A1 WO 1996-AU382 19960621; AU 9661153 A AU 1996-61153 19960621; EP 871470 A1 EP 1996-918517 19960621, WO 1996-AU382 19960621; AU 703052 B AU 1996-61153 19960621; JP 11507927 W WO 1996-AU382 19960621, JP 1997-503469 19960621; AU 9934974 A Div ex AU 1996-61153 19960621, AU 1999-34974 19990611; NZ 310366 A NZ 1996-310366 19960621, WO 1996-AU382 19960621

FDT AU 9661153 A Based on WO 9700695; EP 871470 A1 Based on WO 9700695; AU 703052 B Previous Publ. AU 9661153, Based on WO 9700695; JP 11507927 W Based on WO 9700695; AU 9934974 A Div ex AU 703052

PRAI AU 1995-3780 19950623; AU 1999-34974 19990611

REP 5.Jnl.Ref; EP 409091; EP 499161; WO 8910403; WO 8911864; WO 9110684; WO 9504075

IC ICM A61K038-18; A61K038-22
ICS A61K038-00; A61K038-17; A61K038-19; A61K038-20; A61K045-00; C07K001-14; C12N001-00; C12N005-00; C12N015-09; C12N015-27; C12P021-02

AB WO 9700695 A UPAB: 19970220
A method for inducing apoptosis in cells carrying a haemopoietic growth factor (HGF) heterodimeric receptor, comprising an HGF-specific alpha-chain and betac-chain, comprises contacting the cells with an HGF antagonist to induce apoptosis, where the HGF antagonist comprises a sequence of amino acids within a first alpha-helix, where one or more exposed amino acids in the first alpha-helix of HGF having acidic properties are substd with a basic amino acid residue or a non-acidic amino acid residue.

USE - The method can be used to treat cancers such as myeloid leukaemias and inflammation, eg. rheumatoid arthritis and allergic conditions such as asthma. Induction of apoptosis will also be useful in enrichment of uncommitted progenitors for stem cell transplantation and gene transfer purposes.

ADVANTAGE - The HGF antagonists can specifically bind the alpha-chain of the HGF receptor and such binding induces apoptosis of cells expressing the receptor. Apoptosis occurs even in the presence of the survival factors such as G-CSF and **stem cell factor** (**SCF**) but is prevented by engaging receptor chain betac with IL-3.
Dwg.0/13

FS CPI
FA AB
MC CPI: B04-C01; B04-F0100E; **B14-C03**; B14-C09B; B14-H01A; B14-K01A; B14-L06; B14-S03; D05-H08

L82 ANSWER 25 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1995-351127 [45] WPIX
DNC C1995-153770
TI Reducing the cellular content and activity of NF-kappa B in animals, e.g., for treatment of AIDS - by contacting the cells with an inhibitor of proteasome function or ubiquitin conjugation.
DC B05
IN GOLBERG, A L; MANIATIS, T P; PALOMBELLA, V J; RANDO, O; GOLDBERG, A L
PA (HARD) HARVARD COLLEGE
CYC 62
PI WO 9525533 A1 19950928 (199545)* EN 85p A61K038-06
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SG SI SK TJ TT UA UG UZ VN

AU 9521215 A 19951009 (199603)
EP 750507 A1 19970102 (199706) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
AU 682264 B 19970925 (199802) A61K038-06
JP 09510710 W 19971028 (199802) 86p A61K045-00
ADT WO 9525533 A1 WO 1995-US3315 19950317; AU 9521215 A AU 1995-21215 19950317; EP 750507 A1 EP 1995-914075 19950317, WO 1995-US3315 19950317; AU 682264 B AU 1995-21215 19950317; JP 09510710 W JP 1995-524716 19950317, WO 1995-US3315 19950317
FDT AU 9521215 A Based on WO 9525533; EP 750507 A1 Based on WO 9525533; AU 682264 B Previous Publ. AU 9521215, Based on WO 9525533; JP 09510710 W Based on WO 9525533
PRAI US 1994-210381 19940318
REP 02Jnl.Ref
IC ICM A61K038-06; A61K045-00
ICS A61K031-16; A61K031-27; A61K038-07; A61K038-55; C07K005-06; C07K005-08
ICA C12N009-99
AB WO 9525533 A UPAB: 19971119
Reducing the cellular content and activity of NF-kappa B in animals, comprises contacting cells of the animals with an inhibitor of proteasome function or ubiquitin conjugation.
USE - The transcription factor NF-kappa B plays a central role in the regulation of a diverse set of genes involved in the immune and inflammatory responses. It is required for the expression of, eg., the IL-2 receptor alpha chain gene, the T cell receptor beta chain gene, the TNF- alpha gene, or cytokine genes such as G-**SCF** or IFN- beta .
It is essential for expression of HIV. Cpds. (I) may thus be used in treatment of, eg., inflammation, sepsis or AIDS. Admin. is, e.g., oral, intravenous, intramuscular, topical or by infusion.
Dwg.0/10
FS CPI
FA AB; DCN
MC CPI: B04-C01A; B04-N04A; B10-A19; B10-B01; B10-B02; B10-B03; B10-B04; B14-A02B1; **B14-C03**; B14-L06; B14-S06

L82 ANSWER 26 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1995-240475 [31] WPIX
DNC C1995-110243
TI New lyophilised **stem cell factor** formulations - contg. histidine and/or glutamic acid to provide increased stability and increase shelf-life.
DC B04
IN HERSHENSON, S I
PA (AMGE-N) AMGEN INC
CYC 62
PI WO 9517206 A1 19950629 (199531)* EN 34p A61K038-18
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN
AU 9514422 A 19950710 (199543) A61K038-18
ZA 9410189 A 19951025 (199548) 34p A61K000-00
EP 732935 A1 19960925 (199643) EN A61K038-18
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
NZ 278252 A 19980427 (199823) A61K009-19
AU 696860 B 19980917 (199849) C07K014-00
EP 732935 B1 19981118 (199850) EN A61K038-18
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69414723 E 19981224 (199906) A61K038-18
ES 2123951 T3 19990116 (199909) A61K038-18
US 5965522 A 19991012 (199949) A61K038-18
US 6020469 A 20000201 (200013) C07K001-00
CN 1142771 A 19970212 (200050) A61K038-18
MX 193004 B 19990813 (200063) A61K037-018
CA 2182970 C 20001128 (200067) EN A61K038-18

ADT WO 9517206 A1 WO 1994-US14739 19941221; AU 9514422 A AU 1995-14422 19941221; ZA 9410189 A ZA 1994-10189 19941221; EP 732935 A1 WO 1994-US14739 19941221, EP 1995-906058 19941221; NZ 278252 A NZ 1994-278252 19941221, WO 1994-US14739 19941221; AU 696860 B AU 1995-14422 19941221; EP 732935 B1 WO 1994-US14739 19941221, EP 1995-906058 19941221; DE 69414723 E DE 1994-614723 19941221, WO 1994-US14739 19941221, EP 1995-906058 19941221; ES 2123951 T3 EP 1995-906058 19941221; US 5965522 A Cont of US 1993-172507 19931222, US 1998-106891 19980629; US 6020469 A Cont of US 1993-172507 19931222, Div ex US 1998-106891 19980629, US 1999-292222 19990415; CN 1142771 A CN 1994-195012 19941221; MX 193004 B MX 1995-63 19950102; CA 2182970 C CA 1994-2182970 19941221

FDT AU 9514422 A Based on WO 9517206; EP 732935 A1 Based on WO 9517206; NZ 278252 A Based on WO 9517206; AU 696860 B Previous Publ. AU 9514422, Based on WO 9517206; EP 732935 B1 Based on WO 9517206; DE 69414723 E Based on EP 732935, Based on WO 9517206; ES 2123951 T3 Based on EP 732935

PRAI US 1993-172507 19931222; US 1998-106891 19980629; US 1999-292222 19990415

REP EP 308238; EP 423980; US 5192743; WO 9105795; WO 9200376

IC ICM A61K000-00; A61K009-19; A61K037-018; A61K038-18; C07K001-00; C07K014-00

ICS A61K038-16; C07K001-14; C07K014-435; C07K014-475; C12N000-00

AB WO 9517206 A UPAB: 19950810

A lyophilised **stem cell factor** (**SCF**) formulation contg. histidine and/or glutamic acid is claimed.

USE - The **SCF** formulation can be used in the treatment of haematopoietic, neurological and reproduction related conditions (see WO9105795). It can be used e.g. in the treatment of leukopenia, thrombocytopenia or anaemia, for enhancing engraftment of bone marrow during transplantation, enhancing bone marrow recovery in treatment of radiation, chemical or chemotherapeutic induced bone marrow aplasia or myelosuppression, for treating AIDS, and for sensitising cells to chemotherapy. It can also be used for the treatment of mammals suffering from nerve damage, infertility or intestinal damage. It can further be used in vitro, e.g. for the culture of haematopoietic cells for transfection with DNA.

The histidine and/or glutamic acid increase **SCF** stability and provide formulations with increased shelf-life.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: **B04-H16**; B07-A02B; B10-A07; B10-B02E; B10-B02J; B14-E10; B14-F03; B14-F04; B14-G01B; B14-G02C; B14-J01; B14-N01; B14-P02

L82 ANSWER 27 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1995-155253 [20] WPIX

CR 1997-384670 [35]

DNN N1995-122236 DNC C1995-071533

TI New stem cell proliferation factor - useful for augmenting growth of haematopoietic stem cells.

DC B04 D16 S03

IN DENSLOW, N D; LAWMAN, M J P; LAWMAN, P D

PA (UYFL) UNIV FLORIDA RES FOUND INC

CYC 60

PI WO 9509912 A1 19950413 (199520)* EN 120p C12N015-00
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN
AU 9479299 A 19950501 (199532) C12N015-00
ZA 9407825 A 19951025 (199548) 111p G01N000-00
EP 724632 A1 19960807 (199636) EN C12N015-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 09506245 W 19970624 (199735) 99p C12N015-09
AU 691529 B 19980521 (199832) C12N015-00

ADT WO 9509912 A1 WO 1994-US11339 19941006; AU 9479299 A AU 1994-79299 19941006; ZA 9407825 A ZA 1994-7825 19941006; EP 724632 A1 EP 1994-930058

19941006, WO 1994-US11339 19941006; JP 09506245 W WO 1994-US11339 19941006, JP 1995-511016 19941006; AU 691529 B AU 1994-79299 19941006
FDT AU 9479299 A Based on WO 9509912; EP 724632 A1 Based on WO 9509912; JP 09506245 W Based on WO 9509912; AU 691529 B Previous Publ. AU 9479299, Based on WO 9509912
PRAI US 1993-132994 19931006
REP WO 9320197
IC A61K039-395; C07H015-00; C07K004-00; C12N001-00; C12N005-22; C12N015-02; G01N033-543
ICM C12N015-00; C12N015-09; G01N000-00
ICS A61K038-00; A61K039-395; C07H015-00; C07H021-04; C07K004-00; C07K014-52; C07K016-24; C12N001-00; C12N005-06; C12N005-22; C12N015-02; C12P021-00; C12P021-08; G01N033-53; G01N033-543
ICI C12P021-00, C12R001:
AB WO 9509912 A UPAB: 19970909
Novel stem cell proliferation factor (SCPF) comprises a polypeptide (I) with the following properties: (a) stimulates proliferation of human bone marrow stem cells; and (b) binds SAM.1 antibody which inhibits the stem cell proliferation effect of (a). Also claimed are: (A) an antibody(Ab) that immunospecifically binds to (I), and pref. neutralises the biological activity of (I); (B) a method for producing (I), by (i) culturing a cell that contains a nucleotide sequence encoding (I) under the operational control of a regulatory nucleotide sequence which directs gene expression so that biologically active (I) is expressed by the cultured cell; and (ii) recovering the biologically active cytokine from the culture; (C) a method for producing a cytokine derived from a germ cell tumour line, and stimulates proliferation of human stem cells as in (B); (D) a polynucleotide (PN) sequence encoding (I); (E) a biologically functional expression vector contg. th PN of (D); and (F) a host cell stably transformed with the vector of (E).
USE - (I) (or a cytokine chosen from te group of IL-3, IL-6 and **SCF**) is useful in stimulating the proliferation of human bone marrow stem cells, esp CD34+ cells (claimed). The antibodies may also be used to detect a disorder associated with SCPF, such as leukaemia, aplastic anaemia, neuronal disorder, severe combined immunodeficiency and hypersplenism (claimed). SCPF has been shown to be capable of inducing purified CD34+ cells to enter the cell cycle and proliferate in long term culture. The SCPF may be used to facilitate genetic manipulation of stem cells for use in gene therapy of haematologic disorders including sickle cell anaemia. SCPF may also be used for treatment of conditions that require the growth of stem cell populations, irrespective of their tissue of origin, including hair loss. Removal of SCPF by an antibody may be useful in controlling tumour cell growth.
Dwg.10/21
FS CPI EPI
FA AB; GI
MC CPI: **B04-H16**; B14-F03; B14-H01B; D05-H09; D05-H11A; D05-H12A; D05-H12E; D05-H14; D05-H14B; D05-H17A2
EPI: S03-E14H4

L82 ANSWER 28 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-316651 [39] WPIX
CR 1994-304860 [38]
DNC C1994-144242
TI Compsn. contg. cytokine and muramyl peptide - which induces prodn. of IL-2 receptor antagonist, for treating e.g. allergies, cancer, inflammation, or restoring the haematopoietic system at reduced cytokine doses..
DC B04 B05
IN BAHR, G; CHEDID, L; LEFRANCIER, P
PA (VACS-N) VACSYN SA
CYC 48
PI WO 9421275 A1 19940929 (199439)* 55p A61K037-02
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB HU JP KP KR KZ LK LU LV MG MN MW NL NO NZ PL PT RO RU SD SE SK UA US UZ VN
FR 2703251 A1 19941007 (199440) 29p A61K037-02

AU 9462856 A 19941011 (199504) A61K037-02
EP 689449 A1 19960103 (199606) FR A61K037-02
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 08511235 W 19961126 (199708) 53p A61K038-00
US 5932208 A 19990803 (199937) A61K045-05
ADT WO 9421275 A1 WO 1994-FR307 19940321; FR 2703251 A1 FR 1993-3787 19930331; AU 9462856 A AU 1994-62856 19940321; EP 689449 A1 EP 1994-910445 19940321, WO 1994-FR307 19940321; JP 08511235 W JP 1994-520726 19940321, WO 1994-FR307 19940321; US 5932208 A WO 1994-FR307 19940321, US 1995-522342 19951113
FDT AU 9462856 A Based on WO 9421275; EP 689449 A1 Based on WO 9421275; JP 08511235 W Based on WO 9421275; US 5932208 A Based on WO 9421275
PRAI FR 1993-3230 19930319; FR 1993-3787 19930331
REP 1.Jnl.Ref; EP 228833; EP 257890; EP 329609
IC ICM A61K037-02; A61K038-00; A61K045-05
ICS A01N061-00; A61K037-66; A61K038-21; C07K001-00; C07K009-00; C07K015-00
ICI A61K037-02, A61K037:66; A61K037-02, A61K037:66
AB WO 9421275 A UPAB: 19941122
Compsn. comprises: (1) at least one natural or recombinant cytokine (I), pref. human, and (2) at least one muramyl peptide (II) which, when admin. in vivo together with an interferon (IFN) induces increased prodn. of the IL-1 receptor antagonist IL-1RA but pref. does not induce increase in IL-1, TNF or IL-8. (II) may also be characterised by the fact that when admin. to a human with a (I) which has antineutropaenic and/or antileucopaenic effects it slows down depletion of (even restores) the granulocyte system.
USE/ADVANTAGE - The compsns. are useful in human medicine to treat allergies, cancer, infections and genetic deficiencies which can be compensated by (I). They can also (1) slow down loss of the granulocyte system, where loss occurs spontaneously or as a result of treatment; (2) in conjunction with a cytotoxic agent to restore phagocytes and platelets, and to stimulate bone marrow; (3) for accelerating reconstitution of the haematopoietic system in patients where the immunity system has been destroyed, esp. to permit transplantation; (4) to treat viral nfectinos (esp. HIV in conjunction with AZT or related nucleotides); (5) to treat septic shock (caused by IL-1) and to treat or prevent inflammation (e.g. arthritis or autoimmune diseases); (6) to alleviate effects of treatments or infections that induce IL-1, IL-8 or TNF. Formulation with (II) allows a redn. in the dose of (I) and thus cost and side effects, esp. it makes possible use of (I) which have limited applicaton because of severe side effects. (II) do not stimultae (may even inhibit) prodn. of factors that limit use of IFN but do induce inhibitors of such factors and other cytokines from lymphoid cells. Optimum daily doses of (I) are 1-5 muj/kg for IFN; 1-2 mu/kg for IL-2; and 5-10 microg/kg for granulocyte-macrophage colony stimulating factor (GM-**SCF**). In all cases (II) is 10-350 (pref. 50-200) mg/kg/day.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-H01; B10-A07; B14-A01; B14-A04; **B14-C03**; B14-C09; B14-G02; B14-H01B; B14-S03

L82 ANSWER 29 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-263305 [32] WPIX
DNC C1994-120498
TI New bi cyclic di terpene derivs. - are PAF antagonists, useful for treating allergic and inflammatory diseases.
DC B02 B05 D16
IN CHU, M; GULLO, V P; HORAN, A C; PATEL, M
PA (SCHE) SCHERING CORP
CYC 1
PI US 5338758 A 19940816 (199432)* 8p C07D307-77
ADT US 5338758 A CIP of US 1992-863275 19920403, US 1992-954414 19920930
PRAI US 1992-863275 19920403; US 1992-954414 19920930
IC ICM C07D307-77

ICS A61K031-34
AB US 5338758 A UPAB: 19940928
Bicyclic diterpene derivs. of formulae (I)-(II) are new.
The new cpds. are obtd. by fermentation of Phoma sp. **SCF** 0592, ATCC 74077, in an aq. nutrient medium under submerged aerobic conditions at 27-40 deg. C (pref. 27-35 deg. C), at pH 6.5-8.0, with agitation.
USE - The new cpds. are PAF antagonsists, useful for treating allergic diseaes, e.g. asthma, adult respiratory distress syndrome, urticaria, and inflammatory diseases, e.g. rheumatoid arthritis and osteoarthritis.
Dwg.4/12
FS CPI
FA AB; GI; DCN
MC CPI: B06-A03; B10-J02; **B14-C03**; B14-G02A; B14-K01; B14-L06; D05-C

L82 ANSWER 30 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-100856 [12] WPIX
CR 1995-274849 [36]
DNC C1994-046447
TI Treating damaged or depleted cell populations with cytokine(s) - esp. IL-11 or IL-6, esp. to stimulate gut epithelial cells injured by chemotherapy or radiotherapy..
DC B04 D16
IN CLARK, S C; WILLIAMS, D A
PA (GEMY) GENETICS INST INC
CYC 21
PI WO 9405318 A1 19940317 (199412)* EN 58p A61K037-02
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9350999 A 19940329 (199430) A61K037-02
EP 671934 A1 19950920 (199542) EN A61K037-02
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
US 5460810 A 19951024 (199548) 15p A61K038-18
JP 08500838 W 19960130 (199642) 56p A61K038-00
EP 671934 A4 19961016 (199710) A61K037-02
AU 677236 B 19970417 (199723) A61K037-02
JP 2828778 B2 19981125 (199901) 34p A61K038-00
CA 2142879 C 20001031 (200060) EN A61K038-19
EP 671934 B1 20001220 (200105) EN A61K038-19
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9405318 A1 WO 1993-US8247 19930901; AU 9350999 A AU 1993-50999 19930901; EP 671934 A1 EP 1993-920456 19930901, WO 1993-US8247 19930901; US 5460810 A US 1992-941372 19920902; JP 08500838 W WO 1993-US8247 19930901, JP 1994-507428 19930901; EP 671934 A4 EP 1993-920456 ; AU 677236 B AU 1993-50999 19930901; JP 2828778 B2 WO 1993-US8247 19930901, JP 1994-507428 19930901; CA 2142879 C CA 1993-2142879 19930901, WO 1993-US8247 19930901; EP 671934 B1 EP 1993-920456 19930901, WO 1993-US8247 19930901
FDT AU 9350999 A Based on WO 9405318; EP 671934 A1 Based on WO 9405318; JP 08500838 W Based on WO 9405318; AU 677236 B Previous Publ. AU 9350999, Based on WO 9405318; JP 2828778 B2 Previous Publ. JP 08500838, Based on WO 9405318; CA 2142879 C Based on WO 9405318; EP 671934 B1 Based on WO 9405318
PRAI US 1992-941372 19920902
REP 5.Jnl.Ref; US 5082658; US 5215895; WO 9115227; WO 9305169
IC ICM A61K037-02; A61K038-00; A61K038-18; A61K038-19
ICS A61K038-20
AB WO 9405318 A UPAB: 20010124
Patients with damaged or depleted cell populations are treated by admin. of one of the cytokines interleukin (IL)-=11; IL-6; leukaemia inhibitory factor; oncostatin M and ciliary neurotrophic factor in a pharmaceutical carrier.
Partic. the treatment is applied to epithelial cells (EC) of the small intestine or liver; EC lining the large intestine or stomach; skin,

hair or sperm cells, and can be combined with admin. of other- cytokines.
USE/ADVANTAGE - The treatment is used where damage/depletion has been caused by disease (e.g. Crohns disease); infection, trauma; shock, chemotherapy or radiation therapy. In partic. gut EC are stimulated and in these cases treatment starts before, during or after chemotherapy or radiotherapy (of cancer). IL-11 is already known for treatment of some bone diseases and for (in)directly stimulating prodn. and function of B cells. The cytokine improves integrity of the gut by stimulating stem cells to restore a healthy cell population, preventing entry of bacteria and fungi into the blood. They may also allow higher treatment doses to be given.
Dwg.0/12
Dwg.0/12

FS CPI
FA AB
MC CPI: B04-H02G; B04-H02M; B04-H08; B04-H09; **B04-H16**; B14-N17B; D05-C12; D05-H12; D05-H17C
ABEQ US 5460810 A UPAB: 19951204
Treatment that reduces damage or depletion of gut epithelial cells comprises administration of one or more cytokines, such as interleukin-11 or -6, leukaemia inhibiting factor, oncostatin-M and ciliary neurotrophic factor, dispersed with the usual carriers and opt. additives.
USE - The treatment is a valuable aid to patients after shock, radiation therapy or chemotherapy.
ADVANTAGE - The process enables radiative therapy and/or chemotherapy to be continued for the treatment of cancer and autoimmune diseases.
Dwg.0/2

L82 ANSWER 31 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1992-315933 [38] WPIX
DNC C1992-140336
TI Promoting accelerated wound healing - comprises topical or parenteral administration of granulocyte-, or granulocyte macrophage - colony stimulating factor, pref. in admixture with e.g. interleukin.
DC B04 D16
IN ALTROCK, B W; PIERCE, G
PA (AMGE-N) AMGEN
CYC 23
PI WO 9214480 A1 19920903 (199238)* EN 46p A61K037-02
RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE
W: AU CA FI JP KR NO
AU 9214623 A 19920915 (199251) A61K037-02
ZA 9201237 A 19921125 (199302) 46p A61K000-00
FI 9204778 A 19921021 (199304) A61K000-00
EP 526630 A1 19930210 (199306) EN 46p A61K037-02
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE
NO 9204073 A 19921021 (199307) A61K037-00
PT 100152 A 19930531 (199325) C12N015-00
JP 05506673 W 19930930 (199344) 15p A61K037-02
EP 526630 A4 19930811 (199527) A61K037-02
ADT WO 9214480 A1 WO 1992-US1245 19920219; AU 9214623 A AU 1992-14623 19920219, WO 1992-US1245 19920219; ZA 9201237 A ZA 1992-1237 19920220; FI 9204778 A WO 1992-US1245 19920219, FI 1992-4778 19921021; EP 526630 A1 EP 1992-907847 19920219, WO 1992-US1245 19920219; NO 9204073 A WO 1992-US1245 19920219, NO 1992-4073 19921021; PT 100152 A PT 1992-100152 19920221; JP 05506673 W JP 1992-507313 19920219, WO 1992-US1245 19920219; EP 526630 A4 EP 1992-907847
FDT AU 9214623 A Based on WO 9214480; EP 526630 A1 Based on WO 9214480; JP 05506673 W Based on WO 9214480
PRAI US 1991-659780 19910222; US 1992-821498 19920121
REP 7.Jnl.Ref; US 4810643; WO 9000060; WO 9005755; WO 9008554; WO 9011301
IC ICM A61K037-02; C12N015-00
ICS A61K037-66
AB WO 9214480 A UPAB: 19931113
A method for promoting accelerated wound healing in an injured patient comprises administering, topically or parenterally, an effective amt. of

G-CSF or GM-CSF.
Pref. the CSF is made by recombinant methods, utilising prokaryotic or eukaryotic cells, e.g. E.coli. Pref. the CSF is used in admixture with at least one other protein, selected from recombinant EGF, FGF, G-CSF, GM-CSF, IGF-I, IGF-II, insulin, an interferon, an interleukin, KGF, PO-ECGF, PDGF, **SCF**, TGF-alpha or TGF-beta. The interferon is alpha, beta or gamma-interferon. The interleukin is IL-1, -2, -3, -4, -5, -6, -7, -8, -9 or -10. The admixture is administered in a formulation selected from collagen-based creams, films, microcapsules, powders, lyoluronic acid or other glycosaminoglycans, creams, foams, suture material or wound dressings.
ADVANTAGE - Wounds which heal normally as well as those which resist healing can be treated with G-CSF and Gm-CSF effectively, allowing enhanced healing. Mechanical, thermal, acute, chronic, infected or sterile wounds can be healed8,
Dwg.0/3
FS CPI
FA AB; DCN
MC CPI: B04-B04J; **B12-A07**; D09-C04B
ABEQ JP 05506673 W UPAB: 19931213
A method for promoting accelerated wound healing in an injured patient comprises administering, topically or parenterally, an effective amt. of G-CSF or GM-CSF made by recombinant methods, utilising prokaryotic or eukaryotic cells, e.g. E. coli.
Pref. the CSF is used in admixture with at least one other protein, selected from recombinant EGF, FGF, G-CSF, GM-CSF, IGF-I, IGF-II, insulin, an interferon, and interleukin, KGF, PO-ECGF, pDGF, **SCF**, TGF-alpha or TGF-beta. The interferon is alpha, beta or gamma-interferon. The interleukin is IL-1,-2,-3,-4,-5,-6,-7,-8,-9 or 10. The admixture is administered in a formulation selected from collagen-based creams, films, microcapsules, powders, lyoluronic acid or other glycosaminoglycans, creams, foams, suture material or wound dressings.
ADVANTAGE - Wounds which heal normally as well as those which resist healing can be treated with G-CSF and Gm-CSF effectively, allowing enhanced healing. Mechanical, thermal, acute, chronic, infected or sterile wounds can be healed.

L82 ANSWER 32 OF 32 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1990-354626 [47] WPIX
DNC C1990-154088
TI Compsn. for stimulating growth of human granulocytes - comprises mouse nerve growth factor and opt. human bone marrow.
DC B04 D16
IN YOUNG, M
PA (UYFL) UNIV FLORIDA
CYC 1
PI US 4968618 A 19901106 (199047)*
ADT US 4968618 A US 1988-282500 19881212
PRAI US 1984-672360 19841116; US 1988-282500 19881212
IC C07K015-06; C12N005-00
AB US 4968618 A UPAB: 19930928
Compositions comprises an admixture of an effective amount of a G-CSF selected from nerve growth factor (NGF) and its gamma-subunit, the NGF having molecular weight about 116000 and being derived from mouse submandibular gland or saliva, and a nutrient medium. Preferably the composition also contains human bone marrow. A method for promoting growth of granulocytes from human bone marrow cells by contact with the composition is also claimed.
USE/ADVANTAGE - The compositions stimulate the formation of granulocyte-containing clonies at concentrations as low as 9 x 10 power (-12) without stimulating macrophage growth. NGF and its gamma-subunit can be inexpensively prepared in large amountse unlike prior art G-**SCF** factors. The compositions can be used in treatment of pathologic states, such as leukaemia, where the maturation process is altered.
FS CPI
FA AB

MC CPI: B04-B04J; B12-G05; D05-H08

=> d all abeq tech tot l83

L83 ANSWER 1 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-050109 [06] WPIX
DNC C2001-013835
TI New nucleic acids for treating diseases and disorders, e.g. atherosclerosis, infection, autoimmune diseases, obesity, ear disorders, brain disorders, tumors, diabetes, arthritis, multiple sclerosis and asthma.
DC B04 D16
IN BOSSONE, S; LEIBY, K R; MCKAY, C
PA (MILL-N) MILLENNIUM PHARM INC
CYC 92
PI WO 2000078808 A1 20001228 (200106)* EN 330p C07K014-47
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
ADT WO 2000078808 A1 WO 2000-US16883 20000619
PRAI US 1999-336536 19990618
IC ICM C07K014-47
ICS C07H021-04; C12N001-21; C12N015-63; C12P021-02
AB WO 200078808 A UPAB: 20010126
NOVELTY - Isolated nucleic acid molecules (A) encoding secreted or transmembrane proteins, TANGO 253, 257, and 281 and INTERCEPT 258, are new
DETAILED DESCRIPTION - A new isolated nucleic acid molecule (A) comprising:
(a) a nucleotide sequence 45 % identical to a sequence (I) of 1338, 728, 1869, 1110, 1801, or 735 nucleotides, the cDNA insert of the plasmid with American Type Culture Collection (ATCC) accession number 207222, or a complement;
(b) a fragment of 300 nucleotides of (I) or a sequence of 1831 or 1218 nucleotides, or a complement;
(c) a nucleic acid encoding a polypeptide comprising a sequence (II) of 243, 406, 370 or 245 amino acids, or the amino acid sequence encoded by the cDNA insert of plasmid ATCC 207222;
(d) a nucleic acid encoding a fragment of 15 contiguous amino acids of a polypeptide of 243, 370 or 245 amino acids, or the amino acid sequence encoded by the cDNA insert of plasmid ATCC 207222;
(e) a nucleic acid encoding a naturally occurring allelic variant of a polypeptide comprising (II), which hybridizes to a nucleic acid that has a sequence of 728, 1218, 1110, or 735 nucleotides, or a complement;
(f) a nucleotide sequence that is 95 % identical to a sequence (III) of 1721, or 1218, the cDNA insert of plasmid ATCC 207217, or a complement;
(g) a fragment of 300 nucleotides of (III);
(h) a nucleic acid which encodes a polypeptide (IV) comprising a sequence of 406 amino acids, or the amino acid sequence encoded by the cDNA insert of plasmid ATCC 207217;
(i) a nucleic acid encoding a fragment of (IV), which comprises 360 contiguous amino acids of (IV);
(j) a nucleic acid encoding a naturally occurring allelic variant of (IV) and which hybridizes to a nucleic acid comprising a sequence of 1218 nucleotides, or a complement;
(k) a nucleotide sequence that is 45 % identical to a sequence (V) of 1846 or 1182 nucleotides, the cDNA insert of plasmid ATCC 207221, or a complement;
(l) a fragment of 300 nucleotides of (V);
(m) a nucleic acid encoding a polypeptide (VI) comprising a sequence of 394 amino acids, or the sequence encoded by the cDNA insert of plasmid ATCC 207221;

(n) a nucleic acid encoding a fragment of (VI), comprising 160 contiguous amino acids;

(o) a nucleic acid encoding a naturally occurring variant of (VI) and which hybridizes to a nucleic acid with a sequence of 1182 nucleotides, or a complement;

(p) a nucleotide sequence that is 45 % identical to a sequence (VII) of 1263 or 729 nucleotides, the CDNA insert of plasmid ATCC 207215, or a complement;

(q) a nucleic acid comprising a fragment of 300 nucleotides of (VII);

(r) a nucleic acid encoding a polypeptide (VIII) comprising a sequence of 243 amino acids, or the amino acid sequence encoded by the cDNA insert of plasmid ATCC 207215;

(s) a nucleic acid encoding a fragment of (VIII) comprising 15 contiguous amino acids;

(t) a nucleic acid encoding a naturally occurring allelic variant of (VIII) which hybridizes to a nucleic acid comprising a sequence of 729 nucleotides, or a complement;

(u) a nucleotide sequence that is 95 % identical to a sequence of 1831 or 1218 nucleotides, the cDNA insert of plasmid ATCC 207222, or a complement of them;

(v) a nucleic acid encoding a fragment of 360 contiguous amino acids of a polypeptide comprising a sequence of 406 amino acids, or the sequence encoded by the cDNA insert of plasmid ATCC 207222;

(w) a nucleotide sequence that is 45 % identical to a sequence (IX) of 1858 or 639 nucleotides, or the cDNA insert of plasmid ATCC patent deposit PTA-224, or a complement;

(x) a nucleic acid comprising a fragment of 300 nucleotides of (IX);

(y) a nucleic acid encoding a polypeptide (X) comprising a sequence of 213 amino acids, or the sequence encoded by the cDNA insert of ATCC PTA-224, or a complement;

(z) a nucleic acid encoding a fragment of 15 contiguous amino acids of (X); or

(a') a nucleic acid encoding a naturally occurring allelic variant of (X) which hybridizes to a nucleic acid of 639 nucleotides, or a complement.

All the sequences are given in the specification.

INDEPENDENT CLAIMS are also included for the following:

(1) a host cell containing (A);

(2) an isolated polypeptide (B) comprising:

(a) a fragment of 15 contiguous amino acids of a polypeptide (XI) with a sequence of 243 (2 sequences), 243, 406 (2 sequences), 370, 394, 245 or 213 amino acids;

(b) a naturally occurring allelic variant of (XI) or a sequence encoded by the cDNA insert of plasmids ATCC 207222, 207215, 207217, 207221 and PTA-224, encoded by a nucleic acid that hybridizes to a nucleic acid comprising a sequence of 728, 729, 1218 (2 sequences), 1110, 1182, 735 or 639 nucleotides or a complement; or

(c) a polypeptide encoded by a nucleic acid comprising a sequence 45 or 98 % identical to nucleic acid comprising a sequence of 728, 729, 1110, 1182, 735 or 639 nucleotides, or a complement;

(3) an antibody to (B);

(4) producing a polypeptide that comprises:

(a) a sequence of (XI) or the sequence encoded by the cDNA insert of plasmid ATCC 207222, 207215, 207217, 207221, or PTA-224;

(b) a fragment of (a) of 15 contiguous amino acids; or

(c) a naturally occurring allelic variant of (a) that is encoded by a nucleic acid that hybridizes to a sequence of 1338, 1263, 1831, 1721, 1869, 1846, 1801, or 1858 nucleotides; comprising culturing (1) to express the nucleic acid;

(5) detecting the presence of (B) in a sample comprising contacting the sample with a compound which binds (B) and determining binding;

(6) detecting the presence of (A) in a sample comprising contacting the sample with a nucleic acid probe or primer that hybridizes to the nucleic acid and determining binding;

(7) kits comprising a compound that binds (A) or (B);

(8) identifying a compound which binds (B) comprising contacting (B)

or a cell expressing (B) with a test compound and determining binding;
(9) modulating the activity of (B) comprising contacting (B) or a cell expressing (B) with a compound that binds (B); and
(10) identifying a compound that modulates the activity of (B) comprising contacting (B) with a test compound and determining the effect on the activity.
ACTIVITY - Antiarteriosclerotic; cardiant; vulnerary; antibacterial; virucide; immunosuppressive; anorectic; antiinflammatory; cytostatic; nephrotropic; pulmonary; osteopathic; antidiabetic; antiarthritic; antiallergic; neuroprotective; antiasthmatic; antipsoriatic. No biological data is given.
MECHANISM OF ACTION - Gene therapy.
USE - The nucleic acid molecules are used to produce polypeptides. Compounds which bind the nucleic acids or polypeptides are used to detect them in samples and can be used to modulate the activity of the polypeptide (claimed). The nucleic acids, polypeptides and modulators of them can be used to treat diseases and disorders, such as, atherosclerosis, infection, autoimmune disorders, ear disorders, obesity, brain disorders, tumors, diabetes, arthritis, multiple sclerosis, asthma, psoriasis, and graft/transplant rejections.
Dwg.0/33

FS CPI
FA AB; DCN
MC CPI: B04-E03F; B04-E05; B04-F0100E; B04-G01; B04-N04A0E; B11-C08E; B11-C08E3; B11-C08E5; B12-K04E; B14-A01; B14-A02; B14-C09; B14-E12; B14-F01; B14-F02; B14-F07; B14-G02C; B14-G02D; B14-H01; B14-K01; B14-K01A; B14-N01; B14-N02; B14-N10; B14-N16; B14-N17B; B14-S01; B14-S03; B14-S04; D05-C11; D05-C12; D05-H09; D05-H11; D05-H12A; D05-H14; D05-H17A6
TECH UPTX: 20010126
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Host: The host cell is mammalian or non-mammalian.
Preferred Polypeptide: (B) comprises (XI). It further comprises heterologous amino acid sequences.
Preferred Method: In (5), the compound which binds (B) is an antibody. In (6), the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Nucleic Acid: (A) comprises (I), (III), (V), (VII), (IX) or encodes (II), (IV), (VI), (VIII), (X). It further comprises vector nucleic acid sequences or nucleic acid sequences encoding a heterologous polypeptide.
Preparation: (A) is isolated by standard techniques.

L83 ANSWER 2 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-679487 [66] WPIX
DNN N2000-503009 DNC C2000-206636
TI SECX polypeptides and the nucleic acids that encode them, useful for diagnosing, preventing and treating e.g. cancers, inflammation, arthritis and immunological disorders.
DC B04 D16 S03
IN FERNANDEZ, E; SHIMKETS, R; VERNET, C
PA (CURA-N) CURAGEN CORP
CYC 92
PI WO 2000061754 A2 20001019 (200066)* EN 143p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000042168 A 20001114 (200108) C12N015-12
ADT WO 2000061754 A2 WO 2000-US9392 20000407; AU 2000042168 A AU 2000-42168 20000407
FDT AU 2000042168 A Based on WO 200061754
PRAI US 2000-128514 20000303; US 1999-128514 19990409

IC ICM C12N015-12
ICS A61K031-70; A61K038-17; A61K038-20; A61K039-395; A61K049-00; C07K014-47; C07K014-705; C07K016-18; C07K016-24; C07K016-28; C12N015-24; C12Q001-68; G01N033-68

AB WO 200061754 A UPAB: 20001219
NOVELTY - SECX polypeptides ((I) and (II)) and the nucleic acids ((III) and (IV)) that encode them, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) an isolated polypeptide (pp) (I) comp an amino acid (aa) seq selected from:
(a) a mature form of one of 6 defined aa seqs ((A1)-(A6)) given in the specification;
(b) a variant of a mature forms of (A1)-(A6), in which any aa in the mature form of the sequence (seq) is changed to a different aa (provided that no more than 15% of the aa residues in the seq of the mature form are altered);
(c) the aa seqs (A1)-(A6); and/or
(d) a variant of (A1)-(A6), in which any aa in the mature form of the seq is changed to a different aa (provided that no more than 15% of the aa residues in the seq of the mature form are altered);
(2) an isolated pp (II) comp an aa seq selected from:
(a) a mature form of one of 9 defined aa seqs ((A7)-(A15)) given in the specification; and
(b) the aa seqs (A7)-(A15);
(3) an isolated nucleic acid (na) molecule (III) (or its complement) comprising (comp):
(a) a na seq encoding the pp (I); and/or
(b) a na fragment encoding at least 1 portion of a pp comp (A1)-(A6);
(4) an isolated na molecule (IV) (or its complement) comp:
(a) a na seq encoding the pp (II); and/or
(b) a na fragment encoding at least 1 portion of a pp comp (A7)-(A15);
(5) vectors ((V) and (VI)) comp (I) or (II) (resp);
(6) cells ((VII) and (VIII)) comp (V) or (VI) (resp);
(7) antibodies ((IX) and (X)) that bind immunospecifically to (I) or (II) (respectively (resp));
(8) methods (meths) ((XI) and (XII)) for determining (deting) the presence or amount of (I) or (II) (resp) in a sample (sam), comp:
(a) providing the sam;
(b) contacting the sam with either (IX) or (X) (resp); and
(c) deting the presence or amount of antibody bound to pps to det (det) the presence or amount of pp in the sam;
(9) meths ((XIII) and (XIV)) for deting the presence of or amount of (III) or (IV) (resp) in a sam, comp:
(a) providing the sam;
(b) contacting the sam with a probe that binds to the na molecule; and
(c) deting the presence or amount of probe bound to the na molecule to det the presence or amount of na in the sam;
(10) meths ((XV) and (XVI)) for identifying agent (agt) that binds to (I) or (II) (resp), comp:
(a) contacting the pp with the agt; and
(b) deting whether the agt binds to the pp;
(11) meths ((XVII) and (XVIII)) a meth for identifying a potential therapeutic agt for use in the treatment of a pathology related to aberrant expression or interactions of (I) or (II) (resp), comp:
(a) identifying a pp related to the pathology;
(b) providing a cell expressing the chosen pp and having a property or function due to the action of that pp;
(c) contacting the cell with a composition comp a candidate substance; and
(d) deting whether the substance alters the property or function due to the action of the pp (if the alteration observed in the presence of the substance is not observed when the cell is contacted with a composition devoid of the substance, the substance is identified as a potential

therapeutic agt);

(12) meths ((IX) and (XX)) for modulating the activity of (I) and (II), comp contacting a cell sam expressing the pp with a compound that binds to the pp and modulates its activity;

(13) meths ((XXI) to (XXVI)) of treating or preventing a SECX-associated disorder, comp administering (admin) (I) or (II), (III) or (IV) and/or (IX) or (X) (resp);

(14) compositions comp (I), (II), (III), (IV), (IX) and/or (X);

(15) kits comp the compositions;

(16) the use of (I), (II), (III), (IV), (IX) and/or (X) for the treatment of a human SECX-associated disease or disorder;

(17) meths ((XXVII) and (XXVIII)) for screening for a modulator of latency or a predisposition to an SECX-associated disorder, comp:

(a) admin a test compound to a test animal at increased risk of a SECX-associated disorder (the animal recombinantly expresses (I) or (II));

(b) measuring the activity of (I) or (II) in the animal after admin the test compound;

(c) comparing the activity of the protein in the test animal with the activity of the pp in a control animal not administered (I) or (II) (a change in the activity of (I) or (II) in the test animal relative to the control indicates that the test compound is a modulator of latency of or predisposition to a SECX-associated disorder);

(18) meths ((IXXX) to (XXXII)) for deting the presence of or a predisposition to a disease associated with altered levels of (I), (II), (III) or (IV) in a mammalian subject, comp:

(a) measuring the level of expression of the pp or nas in a sam from the mammalian subject; and

(b) comparing the amount of pp or nas in the sam to the amount of pp or nas present in a control sam from a healthy mammal (an alteration in the level of the pp or nas in the test subject compared to the control indicates the presence or predisposition to the disease); and

(19) meths ((XXXIII) to (XXXVI)) for treating pathological states in mammals, comp admin either a pp at least 95% identical to (I) or (II) (or fragments of them) and/or (IX) or (X).

ACTIVITY - Cytostatic; immunomodulatory; anti-AIDS; immunosuppressive; antimicrobial; antiinflammatory; antiarthritic; dermalogical; antisclerotic; cardiant; neuroprotective; ophthalmological; muscular-general; osteopathic.

MECHANISM OF ACTION - Gene therapy; vaccine.

No biological data given.

USE - The nas and the proteins may be used in the prevention, treatment and diagnosis of diseases associated with inappropriate SECX expression. For example, the SECX pps and nas (and vectors) may be used to treat disorders associated with decreased SECX expression. The nas or vectors may be used to treat diseases by rectifying mutations or deletions in a patient's genome that affect the activity of SECX by expressing inactive proteins or to supplement the patients own production of SECX pps. The nas may be used to produce SECX, according to standard recombinant DNA methology. Antisense na molecules may be administered to down regulate SECX expression by binding with the cells own SECX genes and preventing their expression.

The nas may also be used as DNA probes in diagnostic assays (e.g. polymerase chain reactions (PCR)) to detect and quantitate the presence of similar na seqs in sams, and hence which patients may be in need of restorative therapy.

The SECX pps may be used as antigens in the production of antibodies against SECX pps and in assays to identify modulators (agonists and antagonists) of SECX expression and activity. The anti-SECX antibodies and SECX antagonists may also be used to down regulate SECX expression and activity.

The anti-SECX antibodies may also be used as diagnostic agts for detecting the presence of SECX pps in sams (e.g. by enzyme linked immunosorbant assay (ELISA)) (claimed).

Disorders associated with inappropriate SECX expression include e.g. cancers, inflammation, arthritis and immunological disorders (see specification for full list).

Dwg.0/23
FS CPI EPI
FA AB; DCN
MC CPI: B04-B04C2; B04-B04L; B04-C01; B04-E03F; B04-E04; B04-E05; B04-E06; B04-E08; B04-F0100E; B04-G01; B04-L01; B04-N02A0E; B11-A; B11-C07A4; B11-C08E; B11-C09; B12-K04A; B12-K04E; B12-K04F; **B14-C03**; B14-C09; B14-G03; B14-H01; B14-L01; B14-L06; B14-S03; B14-S11; D05-A01A4; D05-A01B; D05-C12; D05-H07; D05-H08; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12D2; D05-H12D5; D05-H12E; D05-H14; D05-H16; D05-H17A; D05-H18
EPI: S03-E14H
TECH UPTX: 20001219
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptides: If (I) is a variant, it comprises the aa seq of a naturally occurring allelic variant of the pp. The variant is the translation of a single nucleotide polymorphism. Any aa specified in the chosen seq is changed to provide a conservative substitution.
Preferred Nucleic Acids: (III) comprises the nucleotide seq of a naturally occurring allelic na variant and encodes that variant and/or comprises a single nucleotide polymorphism. (III) comprises:
(a) one of 6 defined nucleotide seqs ((N1)-(N6)) given in the specification;
(b) the nucleotide seqs (N1)-(N6) (or their complements) in which 1 nucleotide has been changed (provided that no more than 20% of the nucleotides are changed);
(c) a na fragment of (a); and
(d) a na fragment of (b).
(III) hybridizes to (N1)-(N6) (or their complements) under stringent conditions.
(IV) comprises:
(a) one of 6 defined nucleotide seqs ((N7)-(N15)) given in the specification; and/or
(b) a na fragment of (a) or it complement.
Preferred Vectors: (V) and (VI) further comprise a promoter operably linked to the na molecule.
Preferred Antibodies: (IX) and (X) are monoclonal, humanized antibodies.
Preferred meths: In (XXI) to (XXVI) the subject is human.
In (XXVII) and (XXVIII) the test animal is a recombinant test animal that expresses a test protein transgene or expresses the transgene under the control of a promoter at an increased level relative to a wild-type test animal and the promoter is not the native gene promoter of the transgene.
Preparation: The nas and pps may be prepared according to standard methologies.

L83 ANSWER 3 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-656209 [63] WPIX
CR 1999-443617 [37]
DNC C2000-198613
TI Use of new and known phthalazine derivatives for treating inflammatory rheumatic or rheumatoid disease and/or pain.
DC B03
IN BOLD, G; DAWSON KING, J; FREI, J; HENG, R; MANLEY, P W; WIETFELD, B; WOOD, J M
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH
CYC 92
PI WO 2000059509 A1 20001012 (200063)* EN 122p A61K031-50
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000041125 A 20001023 (200107) A61K031-50
ADT WO 2000059509 A1 WO 2000-EP2726 20000328; AU 2000041125 A AU 2000-41125 20000328
FDT AU 2000041125 A Based on WO 200059509

PRAI GB 1999-16064 19990708; CH 1999-603 19990330
IC ICM A61K031-50
ICS A61P019-02; A61P029-00; C07D401-06; C07D401-12; C07D401-14; C07D471-04
AB WO 200059509 A UPAB: 20010202
NOVELTY - Use of new and known phthalazine derivatives (I) and (I'), their N-oxides or salts for treating inflammatory rheumatic or rheumatoid disease and/or pain is new.
DETAILED DESCRIPTION - Use of phthalazine derivatives of formula (I), their N-oxides or salts for the manufacture of a pharmaceutical preparation for treating inflammatory rheumatic or rheumatoid disease and or pain is new.
r = 0-2;
n = 0-3;
R1, R2 = lower alkyl;
R1+R2 = a bridge of formula (a) (where the bond is achieved via the two terminal C atoms) or (b);
m = 0-4;
one or two of the ring members T1-T4 are N, and the others are in each case CH, and the bond is achieved via atoms T1 and T4;
G = C(O), CHF, CF2, lower alkylene, 2-6C alkenylene, lower alkylene (sic) or 3-6C alkenylene substituted by acyloxy or hydroxy, CH2O, CH2S, CH2NH, CH2OCH2, CH2SCH2, CH2NHCH2, O, S, NH, CH2OCH2, CH2SCH2 or CH2NHCH2;
A, B, D, E, T = N or CH;
provided that at least one and not more than three of A, B, D, E and T are N;
Q = lower alkyl, lower alkoxy or halo;
Ra, Ra' = H or lower alkyl;
X = NH, O, or S;
Y = H, aryl, heteroaryl or optionally substituted cycloalkyl;
Z = mono- or disubstituted amino, halo, optionally substituted alkyl, optionally etherified or esterified hydroxy, nitro, cyano, optionally esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl lower alkylthio, alkylphenylthio, phenylsulfinyl, phenylower alkylsulfinyl, alkylphenylsulfinyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl; or (alternatively or, in a broader aspect of the invention) ureido, halo-lower alkylthio, halo-lower alkansulfonyl, pyrazolyl, lower-alkyl pyrazolyl or 2-7C alkenyl;
the wavy line in group (a) is a single or double bond.
INDEPENDENT CLAIMS are also included for the following:
(1) compounds of formula (I; G = G' and A, B, D, E, T = A', B', D,' E,' T' respectively) (I');
G' = (i) 2-6C alkylenylene, 2-6C alkylene or 3-6C alkenylene substituted by acyloxy or OH, CH2O, CH2S, CH2NH, CH2OCH2, CH2SCH2, CH2NHCH2, O, S, NH, C(O), CHF or CF2; (ii) 2-6C alkylene if Q is lower alkyl; or (iii) 1-6C alkylene if Q is lower alkoxy or halo;
A', B', D,' E,' T' = N or CH, provided that at least one and not more than 3 of them are N, and that T' is only N when (alpha) G' is 2-6C alkenylene or 3-6C alkenylene substituted by acyloxy or hydroxy, or (beta) when Q is lower alkoxy or halo;
(2) preparation of (I');
(3) use of (I') in a diagnostic or therapeutic treatment of the human or animal body;
(4) use of (I') for the preparation of a pharmaceutical composition for treating a disease which responds to an inhibition of angiogenesis;
(5) use of (I') for the preparation of a pharmaceutical composition for treating a disease which responds to an inhibition of VEGF receptor kinase.
ACTIVITY - Antiinflammatory; antirheumatic; antiarthritic; analgesic; cytostatic; antidiabetic; ophthalmological; antipsoriatic; nephrotropic; vasotropic; immunosuppressive; hepatotropic; neuroprotective.
Intradermal administration of 1-(4-chloroanilino)-4-(4-pyridylmethyl)-phthalazine dihydrochloride (a compound (I) known from WO9835958) at 3, 10, and 30 mg/kg once daily from day 15 to day 22 after induction of arthritis, caused 0.8, 12.4 and 37.0 % inhibition of paw swelling in the

therapeutic rat adjuvant arthritis model.

MECHANISM OF ACTION - Vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor; VEGF-dependent cell proliferation inhibitor; angiogenesis inhibitor.

Compounds (I) show IC50 values of 10-100 (especially 10-2000) nM for the inhibition of Flt-1 VEGF receptor tyrosine kinase. Compounds (I) also exhibit ED50 values of 1 nM to 20 micro M (preferably 1-500) nM in VEGF-induced KDR-receptor phosphorylation.

In an assay, E-1-(3-methylanilino)-4-(2-(pyridin-3-yl)vinyl)phthalazine (I'a) and its Z isomer, Z-1-(3-methylanilino)-4-(2-(pyridin-3-yl)vinyl)phthalazine (I'b), exhibited IC50 values of 0.715 and 4.9 micro mol respectively for the inhibition of Flt-1 VEGF receptor tyrosine kinase.

USE - For treating inflammatory rheumatic or rheumatoid disease and/or pain, especially arthritis, particularly rheumatoid arthritis. For treating sequelae or symptoms of inflammation e.g. degeneration (e.g. of cells, synovium or tissues), especially swelling, exudation or effusion or pain. Inflammatory rheumatoid diseases include chronic polyarhthitis, including juvenile arthritis and psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis such as systemic lupus erythematosus, polymyositis, dermatomyositis, systemic scleroderma or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body) or seronegative spondylarthritis e.g. spondylitis ankylosans; vasculitis, sarcoidosis or arthrosis, especially synovial inflammation e.g. synovitis. For diseases associated with deregulated angiogenesis, especially diseases caused by ocular neovascularization, especially retinopathies, e.g. diabetic retinopathy or age related macula degeneration, psoriasis, hemangioblastoma e.g. hemangioma, mesangial cell proliferative disorders such as chronic or acute renal diseases, e.g. diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes or transplant rejection, or especially inflammatory renal disease such as glomerulonephritis, especially mesangioproliferative glomerulonephritis, hemolytic-uremic syndrome, diabetic nephropathy, hypertensive nephrosclerosis, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, fibrotic disorders (e.g. hepatic cirrhosis), diabetes, neurodegenerative disorders and especially neoplastic diseases (e.g. solid tumors, leukemias and other liquid tumors, especially those expressing c-kit, KDR or Flt-1), especially breast cancer, cancer of the colon, lung cancer (especially small cell lung cancer), cancer of the prostate or Kaposi's sarcoma; and as tumor growth inhibitor especially suitable for preventing metastatic spread of tumors and the growth of micrometastases. Also for treating other warm-blooded animals e.g. commercially useful animals e.g. rodents such as mice, rabbits or rats or guinea-pigs. Also for diagnostic purposes, e.g. with tumors that have been obtained form warm-blooded animal 'hosts', especially humans, and implanted into mice to test them for decrease in growth after treatment with such a compound, in order to investigate their sensitivity to the compound and thus improve the detection and determination of possible therapeutic methods for neoplastic diseases in the original host. Can be administered alone or in combination with one or more other therapeutic agents e.g. chemotherapy, radiotherapy, immunotherapy or surgical intervention in the case of tumor therapy.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B14-C01; **B14-C03**; B14-C06; B14-F02D; B14-G02; B14-H01; B14-J01; B14-N03; B14-N10; B14-N12; **B14-N17C**; B14-S04

TECH UPTX: 20001205

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (I) are especially of formula (IA):

r'' = 0 or 1;

n'' = 0-3;

R1'' and R2'' together form a bridge of formula (c);

either each of Z1 and Z2 is H, or one is H and the other is Me, with the binding being achieved via the two terminal CH groups in (c) and to the two adjacent carbon atoms binding R1'' and R2'', so that a six-membered ring is formed;
A'', B'', D'', E'' = CH and T'' = N;
Q'' = Me (preferably bound to A'' and/or D'');
G'' = C(O), CHF or CF2;
Ra'', Ra''' = H;
X'' = imino;
Y'' = e.g. 4-chlorophenyl, 4-tert-butyl phenyl, or (especially if n is other than 0) 4-methylphenyl, 3-methylphenyl, 4-ethyl-phenyl or 3-ethylphenyl.
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I') in which G' = CH2O, CH2NH, CH2S, O, S or NH, are prepared by reacting a compound of formula (II) with a compound of formula HX(CRaRa')nY (III).
L = nucleofugal leaving group.

L83 ANSWER 4 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-464381 [40] WPIX
DNC C2000-139876
TI Novel polypeptides and fusion proteins comprising human tyrosine kinases Lyn A and Lyn B, used to treat or prevent allergic disorders, e.g. drug hypersensitivity, allergic rhinitis, rhinorrhea, or skin eruptions.
DC B04 C06 D16
IN CHEN, H; METZGER, H; VONAKIS, B M
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 6084063 A 20000704 (200040)* 20p C07K007-06
ADT US 6084063 A US 1998-20116 19980206
PRAI US 1998-20116 19980206
IC ICM C07K007-06
ICS C07K014-47
AB US 6084063 A UPAB: 20000823
NOVELTY - Human tyrosine kinases Lyn A and Lyn B polypeptides in a carrier, are new. The polypeptide comprises residues 1-66 of Lyn A (I), or residues 1-45 of Lyn B (II), both sequences fully defined in the specification.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a fusion protein comprising, in a pharmaceutical carrier:
(a) a ligand that binds to and is internalized by cells, which express a high affinity receptor for immunoglobulin E (IgE) on the surface; and
(b) a polypeptide encoded by a nucleic acid encoding (I), residues 1-10, 1-27, or 27-66 of (I), where residues 1-27 have the sequence MetGlyCysIleLysSerLsyGlyLysAspSerLeuSerAspAspGlyValAspLeuLysThrGlnProValArgAsnThr, or five or more contiguous amino acids of (I), where the polypeptide has the same IgE (Fc epsilon RI) receptor binding activity as (I), or its fragments; and
(2) a fusion protein comprising, in a pharmaceutical carrier:
(a) a ligand that binds to and is internalized by cells, which express a high affinity receptor for IgE on the surface; and
(b) a polypeptide encoded by a nucleic acid encoding (II) or five or more contiguous amino acids of (II), where the polypeptide has the same IgE (Fc epsilon RI) receptor binding activity as (II).
ACTIVITY - Antiallergic;antipruritic; antitussive; antiinflammatory; antiasthmatic; immunosuppressive; dermatological. No biological data is given.
MECHANISM OF ACTION - Immunoglobulin E Fc receptor (Fc epsilon RI) inhibitor.
USE - The polypeptides and fusion proteins are useful for treating or preventing allergic disorders and symptoms (e.g. itching, sneezing, coughing, respiratory congestion, rhinorrhea, or skin eruptions) in a subject. These allergic disorders include drug hypersensitivity, allergic rhinitis, bronchial asthma, ragweed pollen hayfever, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, erythema nodosum,

erythema multiforme, Stevens-Johnson Syndrome, cutaneous necrotizing venulitis, bullous skin diseases, allergy to food substances and insect venom-induced allergic reactions. The nucleic acids encoding the fusion proteins are useful for generating transgenic non-human animals in which the nucleic acid encoding the fusion protein is added to the germ line of the animal.
Dwg.0/4

FS CPI
FA AB; DCN
MC CPI: B04-E08; B04-L0400E; B04-N0200E; B11-C08E3; B12-K04A; B14-G02A; B14-K01A; B14-N04; **B14-N17**; C04-E08; C04-L0400E; C04-N0200E; C11-C08E3; C12-K04A; C14-G02A; C14-K01A; C14-N04; **C14-N17**; D05-C03E; D05-H14; D05-H17A3; D05-H17C
TECH UPTX: 20000823
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptide: The fusion protein has a ligand selected from IgE or **c-Kit**.
Preparation: (I), (II) and the fusion proteins are produced by standard recombinant techniques.

L83 ANSWER 5 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-086719 [07] WPIX
DNC C2000-024163
TI In vitro system for studying regulated RNA turnover, containing cell extract and target RNA, for identifying modulators of RNA stability, potential therapeutic agents.
DC A96 B04 D16
IN FORD, L P; WILUSZ, J
PA (UYNE-N) UNIV NEW JERSEY
CYC 86
PI WO 9961605 A2 19991202 (200007)* EN 79p C12N015-10
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9942053 A 19991213 (200020) C12N015-10
ADT WO 9961605 A2 WO 1999-US11581 19990526; AU 9942053 A AU 1999-42053 19990526
FDT AU 9942053 A Based on WO 9961605
PRAI US 1998-86675 19980526
IC ICM C12N015-10
ICS C12P019-34; C12Q001-68
AB WO 9961605 A UPAB: 20000209
NOVELTY - In vitro system (A), able to recapitulate regulated RNA turnover of an exogenous, preselected target RNA (I), comprising a cell extract (II) and (I), is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(a) using (A) to identify agents (B) that modulate the stability of (I) (optionally in presence of exogenous RNA stability modifier), the deadenylation of (I) and/or the deadenylation and degradation of (I);
(b) using (A) to identify, characterize and isolate an endogenous molecule (C) that participates in deadenylation and degradation of (I), or is involved in regulation of these processes;
(c) **kits** for monitoring stability of (I) under conditions that can recapitulate regulated RNA turnover; and
(d) identifying an agent (B') that modulates the degradation of (I) in the absence of deadenylation.
USE - (A) is used to identify agents that modulate stability, deadenylation or degradation of (I), or endogenous molecules that participate in deadenylation/degradation of (I). These modulators are preferably involved in cell growth and differentiation in mammals, especially where these processes are implicated in cell transformation and immune system dysfunction and are potential therapeutic agents, e.g. in conditions associated with abnormal expression of tumor necrosis factor-

alpha , such as sepsis, rheumatoid arthritis or inflammatory bowel disease. (A) can also be used diagnostically to detect the molecular defects in such conditions and for development of improved gene delivery systems.

ADVANTAGE - (A) models in vivo RNA processing, permits high throughput screening of potential modulators and provides accurate and reproducible results.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: A12-V03C2; B04-B03B; B04-C02C; B04-C03A; B04-E02; B04-E03; B11-C08E1; B12-K04A3; B12-K04E; **B14-C03**; B14-C09B; B14-E10C; B14-S06; D05-H09; D05-H12D

TECH UPTX: 20000209

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Process: RNA turnover is regulated by an AU-rich or C-rich element.

Preferred Extract: (II) is isolated from lysed eukaryotic cells or tissues, particularly from HeLa or T cells, or from cells that contain foreign nucleic acids and are infected or stably/transiently transfected. (II) is partially purified and is depleted of proteins that bind polyadenylate (pA). Depletion is achieved by adding a pA competitor RNA, sequestering the proteins, and adding a protease that inactivates the proteins or adding an agent that prevents binding between pA and endogenous binding macromolecules. Proteins are preferably sequestered by adding an antibody that binds pA and/or pA, preferably attached to a matrix.

Preferred Target RNA: (I) may be synthetic, natural, messenger or chemically modified RNA or an RNA-DNA derivative, particularly a 5'-capped and 3'-pA sequence, and may be conventionally labeled.

Preferred System: The system includes an added nucleotide triphosphate (NTP), especially adenosine triphosphate (ATP) and a reaction enhancer (poly(vinyl pyrrolidone), dextran, or preferably poly(vinyl alcohol)).

Preferred Methods: To identify (B) that modulate stability, a test compound is added to (A) and the extent of turnover of (I) is measured, especially from the extent of degradation of labeled (I). The test compound may increase or decrease stability of (I) or modulate the activity of AU- or C-rich element binding proteins, e.g. members of the ELAV protein family. To identify (B) that modulate deadenylation, a similar method is used but (A) contains no NTP and deadenylation of (I) is monitored. Agents that modulate deadenylation and degradation are tested similarly, using system does contain an NTP. To identify (C), a test protein or RNA is added to (A) and the stability of (I) is monitored. To identify (B'), a cell extract containing NTP is treated with test compound and degradation of (I) in the extract is monitored.

Preferred Kits: The kits contain a cell extract free of pA-binding proteins, other reagents and instructions, and optionally NTP, a reaction enhancer and/or (I).

TECHNOLOGY FOCUS - POLYMERS - Preferred reaction enhancers are poly(vinyl alcohol), poly(vinyl pyrrolidone) and dextran.

L83 ANSWER 6 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1999-457574 [38] WPIX

CR 1992-096822 [12]; 1993-368405 [46]

DNC C1999-134203

TI Treating stem cell disorders using soluble **c-kit** ligands.

DC B04

IN BESMER, P; BUCK, J; MOORE, M A S; NOCKA, K

PA (SLOK) SLOAN KETTERING INST CANCER RES

CYC 1

PI US 5935565 A 19990810 (199938)* 80p A61K045-05

ADT US 5935565 A CIP of US 1990-573483 19900827, CIP of US 1990-594306 19901005, CIP of WO 1991-US6130 19910827, Cont of US 1992-873962 19920423, Cont of US 1994-341456 19941117, US 1995-478414 19950607

FDT US 5935565 A Cont of US 5767074

PRAI US 1994-341456 19941117; US 1990-573483 19900827; US 1990-594306 19901005; WO 1991-US6130 19910827; US 1992-873962 19920423; US 1995-478414 19950607
IC ICM A61K045-05
ICS A61K037-00
AB US 5935565 A UPAB: 19990922
NOVELTY - Increasing the level of stem cells in the peripheral blood using a soluble **c-kit** ligand polypeptide and hematopoietic factors, is new.
ACTIVITY - Antianemic; Immunomodulator; Neuroprotective
MECHANISM OF ACTION - Hematopoietic growth factor.
USE - The methods are useful for the treatment of leucopenia, anemia (e.g. Diamond Blackfan anemia (DBA) and aplastic anemia), acquired immune deficiency syndrome (AIDS), nerve damage, and infant exhibiting symptoms of defective lung development, for enhancing bone marrow during transplantation, and for preventing hair loss and loss of hair pigment.
Eleven patients with DBA had decreased mean erythroid burst (BFU-E) frequency with recombinant human erythropoietin (rhEPO) and rhIL-stimulation. Recombinant murine (rm) KL was added, either to or substituted for rhIL resulting in all patients showing significant increases in BFU-E size and hemoglobinization. The combination of rhEPO, rhIL, and rmKL at least doubled mean BFU-E in 8 of the 11 patients.
DESCRIPTION OF DRAWING(S) - The diagram shows the proliferative response of +/+ (wild-type) and W/WV (white-spot) bone marrow derived mast cells (BMMCs) to fibroblast conditioned medium and IL-3.
Dwg.1/35
FS CPI
FA AB; GI; DCN
MC CPI: B04-H02A; B04-H02C; B04-H02G; B04-H04A; B04-H04C; B14-F03; B14-G01B; B14-G03; B14-H01A; B14-K01; **B14-N17**
TECH UPTX: 19990922
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Hematopoietic Factor: The hematopoietic factor is interleukin 1 (IL-1), interleukin 3 (IL-3), interleukin 6 (IL-6), granulocyte macrophage-colony stimulating factor (GM-CSF), and/or granulocyte-colony stimulating factor (G-CSF). The hematopoietic factor is especially IL-1 and GM-CSF, IL-1 and G-CSF, IL-1 and IL-3, IL-1, IL-6 and GM-CSF, or IL-1, IL-3 and IL-6.

L83 ANSWER 7 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-312933 [26] WPIX
DNC C1999-092373
TI New azaoxindole derivatives useful for treating diseases characterized by a cellular proliferation.
DC B02
IN CHEUNG, M; GLENNON, K C; LACKEY, K E; PEEL, M R
PA (GLAX) GLAXO GROUP LTD
CYC 84
PI WO 9921859 A1 19990506 (199926)* EN 133p C07D471-04
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9911510 A 19990517 (199939) C07D471-04
ZA 9809249 A 20000628 (200037) 133p C07D000-00
ADT WO 9921859 A1 WO 1998-EP6357 19981008; AU 9911510 A AU 1999-11510 19981008; ZA 9809249 A ZA 1998-9249 19981009
FDT AU 9911510 A Based on WO 9921859
PRAI GB 1997-21437 19971010
IC ICM C07D000-00; C07D471-04
ICS A61K031-435
ICI C07D209:00, C07D221:00, C07D471-04
AB WO 9921859 A UPAB: 19990707
NOVELTY - Novel azaoxindole derivatives (I) are protein kinase inhibitors useful for treating diseases characterized by a cellular proliferation.

DETAILED DESCRIPTION - Azaoxindole derivatives of formula (I) and their salts, biohydrolysable esters, amides, carbamates, carbonates, or ureides, solvates, hydrates, affinity reagents and prodrugs are new.

R1 = Het, aryl or biaryl (all optionally substituted by 1-4 R5, COR5, COOR5 and/or OR5);

R2 = H, Het, fused Het, aryl, 1-12C aliphatic, CN, NO2, halo, OR5, SR5, SOR5, NR5R7, NR5COR5, NR5CO2R5, NR5CONR5R7, NR5SO2R5, NR5C(NR5)NHR5, COR5, CO2R5, CONR5R7, SO2NR5R7, OCONR5R7 or C(NR5)NR5R7; the 1-12C aliphatic optionally bears one or two chains selected from CO, O, S, SO, SO2 or NR5; and the Het, fused Het, aryl or 1-12C aliphatic are optionally substituted by 1-3 R5;

R3 = H, Het, fused Het, aryl, 1-12C aliphatic, CN, NO2, halo, OR5, SR5, SOR5, NR5R7, NR5COR5, NR5CO2R5, NR5CONR5R7, NR5SO2R5, NR5C(NR5)NHR5, COR5, CO2R5, CONR5R7, SO2NR5R7, aryl-SO2NR5R7, OCONR5R7 or C(NR5)NR5R7; in which the 1-12C aliphatic optionally bears one or two chains selected from CO, O, S, SO, SO2 or NR5; and the Het, aryl or 1-12C aliphatic are optionally substituted by 1-3 R5;

R4 = H, Het, fused Het, aryl, 1-12C aliphatic, CN, NO2, halo, OR5, SR5, SOR5, NR5R7, NR5COR5, NR5CO2R5, NR5CONR5R7, NR5SO2R5, NR5C(NR5)NHR5, COR5, CO2R5, CONR5R7, SO2NR5R7, OCONR5R7 or C(NR5)NR5R7; the 1-12C aliphatic optionally bears one or two chains selected from CO, O, S, SO, SO2 or NR5; and the Het, fused Het, aryl or 1-12C aliphatic are optionally substituted by 1-3 R5;

R2+R3 or R3+R4 = fused ring selected from 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings; the heterocyclic rings having 1-3 heteroatoms, selected from 0-3 N, and 0-1 O or S; and the fused ring is optionally substituted by 1-3 R5;

R5 = H, Het, aryl, halo or 1-12C aliphatic (optionally bearing one or two chains selected from O, S, SO, SO2 or NR6); the 1-12C aliphatic, aryl or Het are optionally substituted by 1-4 halo, another Het or substituted Het, aryl or substituted aryl, CN, NO2, R6, SR6, OR6, N(R6)2, SOR6, SO2R6, SO2N(R6)2, NR6COR6, NR6CON(R6)2, NR6(NR6)NHR6, CO2R6, CON(R6)2, NR6SO2R6, OCON(R6)2 or NR6CO2R6; the substituted Het and substituted aryl are substituted by CN, NO2, R6, SR6, OR6, N(R6)2, SOR6, SO2R6, SO2N(R6)2, NR6COR6, NR6CON(R6)2, NR6(NR6)NHR6, CO2R6, CON(R6)2, NR6SO2R6, OCON(R6)2 or NR6CO2R6;

R6 = H or 1-12C aliphatic, Het or aryl (optionally substituted by 1-3 halo or OH);

R7 = H or R5; and

Het = acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithione, dithiazine, dithiazole, dithiolane, furan, imidazole, imdazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiozole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxaine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, or trithiane.

ACTIVITY - Cytostatic; Immunosuppressive; Antirheumatic; Antiarthritic; Antiinflammatory; Antiasthmatic; Antidiabetic.

3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydropyrrolo(2,3-6) pyridin-2-one exhibited an IC50 value of 1 microns m against raf kinase.

MECHANISM OF ACTION - Protein kinase inhibitor.

USE - (I) are useful in the treatment of a disease mediated by a mitogen activated protein kinase such as abl, ATK, bcr-abl, Blk, Brk, BEK, **C-kit**, C-met, C-src, CDK1, CDK2, CDK4, CDK6, cR of 1, CSF 1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, Fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, Gsk, Hck, IGF-IR, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PlK, FKO, PYK2, ros,

tie1, tie2, TRK, UL97, Yeo, Sap70 or VEGFR. (I) are thus useful for treating restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation and neurodegenerative disease and for inhibiting tumor growth and preventing organ transplant rejection and healing a chronic wound.

FS CPI
FA AB; GI; DCN
MC CPI: **B14-C03**; B14-C09; B14-D06; B14-F01B; B14-F02D; B14-F07; B14-G02C; B14-H01B; B14-J01; B14-K01A; B14-N10; B14-N12; B14-N17B; **B14-N17C**; B14-S04
TECH UPTX: 19990707
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) can be prepared by reacting azaoxindole derivatives (II) with aldehyde derivatives (III).

L83 ANSWER 8 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-263461 [22] WPIX
DNC C1999-077660
TI New substituted oxindole derivatives.
DC B02
IN DAVIS, S T; DICKERSON, S H; FRYE, S V; HARRIS, P A; HUNTER, R N; KUYPER, L F; LACKEY, K E; LUZZIO, M J; VEAL, J M; WALKER, D H
PA (GLAX) GLAXO GROUP LTD
CYC 84
PI WO 9915500 A1 19990401 (199922)* EN 133p C07D209-40
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9897407 A 19990412 (199934) C07D209-40
ZA 9808078 A 20000531 (200032) 130p C07D000-00
EP 1009738 A1 20000621 (200033) EN C07D209-40
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2000000798 A3 20000816 (200048) C07D209-40
BR 9812048 A 20000926 (200051) C07D209-40
ADT WO 9915500 A1 WO 1998-EP5559 19980903; AU 9897407 A AU 1998-97407 19980903; ZA 9808078 A ZA 1998-8078 19980903; EP 1009738 A1 EP 1998-951342 19980903, WO 1998-EP5559 19980903; CZ 2000000798 A3 WO 1998-EP5559 19980903, CZ 2000-798 19980903; BR 9812048 A BR 1998-12048 19980903, WO 1998-EP5559 19980903
FDT AU 9897407 A Based on WO 9915500; EP 1009738 A1 Based on WO 9915500; CZ 2000000798 A3 Based on WO 9915500; BR 9812048 A Based on WO 9915500
PRAI GB 1997-18913 19970905
IC ICM C07D000-00; C07D209-40
ICS A61K031-40; A61P009-00; A61P035-00; C07D209-34; C07D401-06; C07D401-12; C07D403-04; C07D403-12; C07D405-12; C07D413-04; C07D471-04; C07D487-04; C07D491-04; C07D498-04; C07D513-04
ICI C07D209:00; C07D263:00, C07D498-04; C07D231:00, C07D487-04; C07D249:00, C07D487-04; C07D209:00, C07D487-04; C07D209:00, C07D263:00, C07D498-04; C07D209:00, C07D231:00, C07D487-04; C07D209:00, C07D249:00, C07D487-04; C07D209:00, C07D487-04; C07D221:00, C07D471-04; C07D209:00, C07D317:00, C07D491-04
AB WO 9915500 A UPAB: 19990609
NOVELTY - Substituted oxindole derivatives (I) are new.
DETAILED DESCRIPTION - Substituted oxindole derivatives of formula (I) and their salts, biohydrolyzable esters, biohydrolyzable amides or carbamates, solvates, hydrates, affinity reagents or prodrugs in either crystalline or amorphous form are new:
X = N, CH, CCF3 or C(1-12C aliphatic);
R1 = H, 1-12C aliphatic, thiol, hydroxy, hydroxy-(1-12C aliphatic), Aryl, Aryl-(1-12C) aliphatic, R6-Aryl-(1-12C) aliphatic, Cyc, Cyc-1-6C aliphatic, Het, Het-(1-12C) aliphatic, 1-12C alkoxy, Aryloxy, amino, 1-12C

aliphatic-amino, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic aminocarbonyl, di-(12C) aliphatic-aminosulfonyl, 1-12C alkoxycarbonyl, halo, cyano, sulfonamide or nitro;

R2 = H, 1-12C aliphatic, N-hydroxyimino-(1-12C) aliphatic, 1-12C alkoxy, hydroxy-(1-12C) aliphatic, 1-12C alkoxycarbonyl, carboxyl-(1-12C) aliphatic, Aryl, R6-Aryl-oxycarbonyl, R6-oxycarbonyl-Aryl, Het, aminocarbonyl, 1-12C aliphatic-aminocarbonyl, Aryl-(1-12C) aliphatic aminocarbonyl, R6-Aryl-(1-12C) aliphatic-aminocarbonyl, Het-(1-12C) aliphatic-aminocarbonyl, hydroxy-(1-12C) aliphatic-aminocarbonyl, 1-12C alkoxy-(1-12C) aliphatic-aminocarbonyl, 1-12C alkoxy-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-aminocarbonyl, di-(1-12C) aliphatic-aminosulfonyl, halo, hydroxy, nitro, 1-12C aliphatic-sulfonyl, aminosulfonyl or 1-12C aliphatic-aminosulfonyl; or

R1 + R2 = a fused ring chosen from Het (optionally substituted by halo, nitro, cyano, 1-12C alkoxy, carbonyl-(1-12C) alkoxy or oxo);

R3 = H, 1-12C aliphatic, hydroxy, hydroxy(1-12C) aliphatic, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-aminocarbonyl, di(1-12C) aliphatic-aminosulfonyl, 1-12C alkoxy, Aryl, Aryloxy, hydroxyl-Aryl, Het, hydroxy-Het, Het-oxy or halo; or

R2 + R3 = a fused ring chosen from Het (optionally substituted by 1-6C aliphatic or 1-6C aliphatic carbonyl;

R4 = sulfonic acid, 1-12C aliphatic sulfonyl, sulfonyl-(1-12C) aliphatic, 1-12C aliphatic sulfonyl(-16C) aliphatic, 1-6C aliphatic-amino, R7-sulfonyl, R7-sulfonyl(1-12C) aliphatic, R7-aminosulfonyl, R7-aminosulfonyl-(1-12C) aliphatic, R7-sulfonylamino, R7-sulfonylamino-(1-12C) aliphatic, aminosulfonylamino, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-aminocarbonyl, di-(1-12C) aliphatic-aminosulfonyl, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-amino-(1-12C) aliphatic, (R8)1-3-Aryl-amino, (R8)n-Aryl-sulfonyl, (R8)n-Aryl-aminosulfonyl, (R8)n-Aryl-sulfonylamino, Het-amino, Het-sulfonyl, Het-aminosulfonyl, aminoiminoamino or aminoiminoaminosulfonyl;

n = 1-3;

R5 = H; or

R4 and R5 = Het (optionally substituted by 1-12C aliphatic, oxo or dioxo);

R6 = 1-12C aliphatic, hydroxy, 1-12C alkoxy or halo;

R7 = H, 1-12C aliphatic, 1-12C alkoxy, hydroxy-(1-12C) alkoxy, hydroxy-(1-12C) aliphatic, carboxylic acid, 1-12C aliphatic carbonyl, Het, Het-(1-12C) aliphatic, Het-(1-12C) alkoxy, di-Het-(1-12C)alkoxy-Aryl, Aryl-(1-12C)aliphatic, Aryl-(1-12C)alkoxy, Aryl-carbonyl, 1-18C alkoxyalkoxyalkoxyalkoxyaliphatic or hydroxyl;

R8 = H, nitro, cyano, 1-12C alkoxy, halo, carbonyl-(1-12C) alkoxy or halo-(1-12C) aliphatic;

Aryl = phenyl, naphthyl, phenanthryl or anthracenyl;

aliphatic = alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene (disclosed);

Cyc = cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl (all optionally unsaturated); and

Het = optionally saturated heterocycle chosen from benzimidazole, didhydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thiophene, thiopyran, triazine or triazole.

provided that:

(a) R1-R3 may not all be H; and

(b) when R2 = thiadiazine, R4 cannot be methylsulfone.

ACTIVITY - Immunosuppressant, anticancer, anti-arthritic, anti-angiogenic, anti-cirrhotic, anti-atherosclerotic, renal, anti-psoriatic, anti-diabetic, anti-inflammatory, neuroactive, anti-hyperproliferative.

MECHANISM OF ACTION - Protein kinase inhibitor; protein kinase antagonist.

CDK1 and CDK2 were expressed using a baculovirus expression system and were purified partially to comprise 20-80% of total protein with no detectable competing reactions present. Assays were performed by incubating either enzyme (0.2-10 nM), with and without inhibitor, one of the two peptide substrates (1-10 nM), (gamma 32P)ATP (1-120 nM) and magnesium ions (10-20 nM) for 10-120 minutes. Reactions were terminated with 0.2-2 volumes of either acetic acid or 50-100 mM EDTA buffered to pH 7. The buffer employed was either 30 mM HEPES 7.4 containing 0.15 M sodium chloride and 5% dimethylsulfoxide (DMSO), the buffer 50 M MOPS 7.0 containing 0.15M sodium chloride and 5% DMSO or the buffer 100 mM HEPES 7.5 containing 0.1 mg/ml bovine serum albumin and 5% DMSO. Inhibitors were diluted in 100% DMSO prior to addition into the assay. Detection of peptide phosphorylation was accomplished by scintillation counting. Counts detected minus the appropriate background (assays with additional 40 mM EDTA or lacking peptide substrate) were assumed to be proportional to the reaction initial rates and IC50 values were determined by a least squares fit to the equation CPM = Vmax asterisk (1-(I)/(K+(I))))+nsb. Twelve compounds were tested against CDK2 and CDK1. Against CDK2, IC50 values were 51-100 nM (n=1), 11-50 nM (n=3) and 1-10 (n=8) and against CDK1 were greater than 100 (n=2), 51-100 nM (n=3), 11-50 nM (n=5) and 1-10 (n=2).

USE - Used for the treatment of diseases mediated by kinases such as abl, ATK, bcr-abl, Blk, Brk, Btk, **c-kit**, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFT, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, HCckk, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFFR, PIK, PJKC, PYJK2, ros, tie1, tie2, TRK, Yes and Zap70 as well as cyclin-dependent kinases (claimed). Used to treat organ transplant rejection, chemotherapy-induced alopecia or thrombocytopenia, to inhibit tumor growth, and to treat mucositis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic angiopathy, glomerulopathy, psoriasis, diabetes mellitus, inflammation, neurodegenerative diseases, macular degeneration, actinic keratosis and hyperproliferative disorders (claimed). Also used for the treatment of viral or eukaryotic infections including those caused by cytomegalovirus and human papillomavirus.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B14-A02; **B14-C03**; B14-C09B; B14-F02D; B14-F07; B14-H01; B14-N03; B14-N10; B14-N12; **B14-N17C**; B14-R02; B14-S04
TECH UPTX: 19990609

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by reacting 2-oxoindoline derivative of formula (II) with an aniline derivative of formula (III).

L83 ANSWER 9 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-229499 [19] WPIX
CR 1999-229532 [19]; 1999-229533 [19]; 1999-254381 [19]; 1999-302739 [24]; 1999-326705 [25]; 1999-337420 [25]; 1999-347718 [29]; 1999-371118 [30]; 1999-404743 [29]; 1999-430385 [35]; 1999-551358 [46]; 1999-580306 [47]; 1999-620728 [53]; 2000-072883 [05]; 2000-116314 [09]; 2000-237871 [20]; 2000-271386 [23]; 2000-271431 [23]; 2000-271434 [23]; 2000-271435 [23]; 2000-292842 [24]; 2000-431586 [37]
DNN N1999-169851 DNC C1999-067532
TI Composition containing novel polypeptide PRO245, its agonist or antagonist.
DC B04 D16 S03
IN FONG, S; GODDARD, A; GURNEY, A L; TUMAS, D; WOOD, W I
PA (GETH) GENENTECH INC
CYC 82
PI WO 9914241 A2 19990325 (199919)* EN 176p C07K014-705
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG

MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9893959 A 19990405 (199933)
ADT WO 9914241 A2 WO 1998-US19437 19980917; AU 9893959 A AU 1998-93959 19980917
FDT AU 9893959 A Based on WO 9914241
PRAI US 1998-88026 19980604; US 1997-59119 19970917; US 1997-59263 19970918; US 1997-63550 19971028; US 1997-65186 19971112; US 1997-66364 19971121; US 1997-66770 19971124
IC ICM C07K014-705
ICS A61K038-17; C07K016-28; G01N033-53
AB WO 9914241 A UPAB: 20000807
NOVELTY - Composition containing (apart from a carrier or excipient), a novel PRO245 polypeptide (I), its agonist or antagonist, or their fragments, for modulating:
(i) infiltration of inflammatory cells into tissue;
(ii) an immune response; or
(iii) T cell proliferation.
DETAILED DESCRIPTION - The composition increases or decreases any of the effects (i)-(iii).
INDEPENDENT CLAIMS are also included for the following:
(a) detecting (I) from its binding to specific antibodies (Ab);
(b) diagnosis of immune-related diseases by detecting elevated expression of the gene encoding (I) in tissues;
(c) **kits** for this diagnosis containing Ab or its fragments; and
(d) method for identifying agents (A) that inhibit expression or activity of (I).
ACTIVITY - Anti-inflammatory; anti-autoimmune; anti-diabetic; anti-allergic; anti-asthmatic; antiviral; immunomodulating.
MECHANISM OF ACTION - (I) and its (ant)agonists are immunosuppressants or immunostimulants. Peripheral blood mononuclear cells (PBMC) were isolated from the spleen of mice, resuspended at 10 million/ml, and 50 mu l of the suspension incubated with 50 mu l stimulator cells (irradiated PBMC) and 0.1 ml solution containing 0.1 or 1% PRO245. After 4 days at 37 deg. C, the cells were pulsed with tritiated thymidine and 6 hr later incorporation of radioactivity measured. The percentage incorporation, relative to an untreated control, was 190-194% at 0.1% PRO245 and 212-300% at 1%, i.e. stimulation of proliferation of stimulated T cells.
USE - (I), and its (ant)agonists and their fragments, are used to treat immune-related diseases, particularly T cell-mediated diseases. The diseases treated include systemic lupus erythematosis, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathies, systemic sclerosis (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), Sjsgren's syndrome, systemic vasculitis, sarcoidosis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura immune-mediated thrombocytopenia), thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis), multiple sclerosis, idiopathic demyelinating polyneuropathy, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis, inflammatory bowel disease (ulcerative colitis: Crohn's disease), gluten-sensitive enteropathy, and Whipple's disease. Autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme,contact dermatitis, psoriasis, asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity, urticaria, eosinophilic pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and transplantation associated diseases (graft rejection, and graft-versus-host-disease) (claimed).
(I), its (ant)agonists or fragment can also be used as an adjuvant in

treatment of tumors. Antibodies against (I) can also be used for diagnosing such diseases.
Dwg.0/41
FS CPI EPI
FA AB; DCN
MC CPI: B04-E02A; B04-E02F; B04-F01; B04-G01; B04-N04; B04-P0100E; B12-K04; **B14-C03**; B14-G02D; B14-H01; D05-H09; D05-H11A; D05-H12A; D05-H12E; D05-H14; D05-H16A; D05-H17A2
EPI: S03-E14H4
TECH UPTX: 19990510
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred compositions: These contain antagonistic Ab, preferably monoclonal, optionally in single-chain form, or their fragments, optionally with non-human complementarity determining regions in a human framework.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: Ab are produced by standard methods of immunization or cell fusion, using as immunogen recombinant (I), their fusions or cells that express them. Ab may be conjugated, to each other, toxins, chemotherapy agents or radioisotopes, by usual methods of chemical conjugation.
Preferred assays: (I) is detected by standard immunoassay with Ab. To identify (A), the test compound, preferably labeled, and (I), preferably immobilized, are incubated together and any interaction between them measured. Typical (A), other than Ab, include (phospho)peptides, antisense molecules, ribozymes and triplex-forming agents.
Isolation; The extracellular domains of about 950 known secreted proteins were used to search expressed sequence tag (EST) databases and a 414 bp consensus sequence assembled, encoding a protein with some similarity with transmembrane protein receptor tyrosine kinases. Based on this sequence the polymerase chain reaction (PCR) primers (P1), and (P2) were designed along with the 48 bp probe (P3).
(1) 5'ATCGTTGTGAAGTTAGTGCCCC3' (P1);
(2) 5'ACCTGCGATATCCAACAGAATTG3' (P2); and
(3) 5'GGAAGAGGATACAGTCACTCTGGAAGTATTAGTGGCTCCAGCAGTTCC3' (P3).
The primers were used to amplify libraries derived from fetal liver RNA and clones isolated from a positive library using (P3) and one of the primers. Full-length cDNA 1295 bp sequence (given in the specification), encoding a 312 amino acid precursor with 60% identity with the human c-myc sequence was isolated. This clone has been deposited as ATCC 209265. Essentially similar methods were used to isolate six other protein-encoding sequences. Once isolated the cDNA can be expressed in usual vector/host systems, e.g. Escherichia coli, yeast, mammalian or yeast cells.

L83 ANSWER 10 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-190570 [16] WPIX
DNC C1999-056099
TI New benzylidene-di hydro-indolone derivatives - useful as tyrosine kinase inhibitors, e.g. for treating cancer, rheumatoid arthritis or diabetes mellitus.
DC B02
IN DICKERSON, S; HARRIS, P A; HUNTER, R N; JUNG, D K; LACKEY, K E; MCNUTT, R W; PEEL, M R; VEAL, J M
PA (GLAX) GLAXO GROUP LTD
CYC 84
PI WO 9910325 A1 19990304 (199916)* EN 142p C07D209-34
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9891584 A 19990316 (199930) C07D209-34
ZA 9807037 A 20000426 (200027) 141p C07D000-00
EP 1003721 A1 20000531 (200031) EN C07D209-34
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

ADT WO 9910325 A1 WO 1998-EP4844 19980804; AU 9891584 A AU 1998-91584 19980804; ZA 9807037 A ZA 1998-7037 19980805; EP 1003721 A1 EP 1998-943832 19980804, WO 1998-EP4844 19980804
FDT AU 9891584 A Based on WO 9910325; EP 1003721 A1 Based on WO 9910325
PRAI GB 1997-16557 19970806
IC ICM C07D000-00; C07D209-34
ICS A61K031-40; C07D401-04; C07D401-06; C07D401-12; C07D403-04; C07D403-06; C07D405-06; C07D413-04; C07D413-06; C07D417-04; C07D417-06; C07D471-04
ICI C07D209:00, C07D221:00, C07D471-04; C07D221:00, C07D235:00, C07D471-04
AB WO 9910325 A UPAB: 19990424
NOVELTY - 3-Benzylidene-1,3-dihydro-indol-2-one derivatives (I) are new.
DETAILED DESCRIPTION - Dihydro-indolone derivatives of formula (I) and their salts, biohydrolysable esters, amides, carbamates, carbonates and ureides and solvates, hydrates, affinity reagents and prodrugs are new. R1 = H; or R1 + R2 or R2 + R3 = 5- to 10-membered aryl, heteroaryl or heterocyclyl having 0-3 N and 0 or 1 O or S (optionally substituted by 1-3 R9); R2, R3 = H, Het, aryl, A, CN, NO2, halo, R10, OR10, SR10, SOR10, SO2R10, NR10R11, NR11R12, NR12COR11, NR12CO2R11, NR12CONR11R12, NR12SO2R11, NR12C(NR12)-NHR11, COR11, CO2R11, CONR12R11, SO2NR12R11, OCONR12R11 or C(NR12)NR12R11; in which (i) A optionally bears one or two CO, O, S, SO, SO2 or NR12; and (ii) Het, aryl and A are optionally substituted by 1-3 R10; A = 1-12C aliphatic group; R4 = H, halo, NO2 or CN; R5 = H, or A optionally substituted by 1-3 halo, OH or aryl; R6, R7 = halo, CN, NO2, CONR10R11,O2NR10R11, NR10R11 or OR11; R8 = OH, NHSO2R12 or NHCOCF3; R9 = H, A, CN, NO2, R10, OR10, SR11, OR11, SOR10, SO2R10, NR10R11, NR11R12, NR12COR11, NR12CO2R11, NR12CONR11R12, NR12SO2R11, NR12C(NR12)-NHR11, CO2R11, CONR12R11, SO2NR12R11, OCONR12R11 or C(NR12)NR12R11; R10 = H or halo; or A, aryl or Het (all optionally substituted by 1-3 halo, another Het, aryl, CN, SR12, OR12, N(R12)2, SOR12, SO2R12, SO2N(R12)2, NR12COR12, NR12CO2R12, NR12CON(R12)2, NR12(NR12)NHR12, CO2R12, CON(R12)2, NR12SO2R12 or OCON(R12)2); in which A optionally bears one or two O, S, SO, SO2 or NR12; R11 = H or R10; R12 = H, A (optionally substituted by 1-3 halo or OH) or Het; Het = benzofuran, benzoxazole, dioxin, dioxan, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, indole, indazole, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, quinazoline, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine or triazole.
USE - (I) are tyrosine kinase inhibitors (claimed) and aberrant cellular proliferation inhibitors. They can be used for treating disorders mediated by protein kinase activity, a mutated ras gene, an upregulated tyrosine kinase signalling pathway, a mitogen activated protein kinase, cRaf kinase (especially cRaf1 kinase) or a kinase selected from abl, ATK, bcr-abl, Blk, Brk, Btk, **c-kit**, c-met, c-src, CDK1, CDK2, CDK4, CDK6, CSFIR, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, Hck, IGF-IR, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PlK, PKC, PYK2, ros, tie1, tie2, TRK, Yes or Zap70 (all claimed). (I) are used for inhibiting tumour growth; preventing organ transplant rejection; healing chronic wounds; or treating restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, diabetes mellitus, inflammation or neurodegenerative diseases (all claimed).
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-D01; B14-C09; B14-D05; B14-H01B; B14-S04

L83 ANSWER 11 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-059656 [05] WPIX
DNC C1999-017493

TI Hetero- and carbo- arylidene indolinone protein kinase modulators - used to affect signal transduction, for treatment of e.g. cancer, diabetes and angiogenesis.
DC B02
IN HIRTH, K P; MCMAHON, G; SHAWVER, L K; SUN, L; TANG, P C; BLAKE, R A
PA (SUGE-N) SUGEN INC
CYC 83
PI WO 9850356 A1 19981112 (199905)* EN 268p C07D207-09
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9876842 A 19981127 (199915) C07D207-09
EP 984930 A1 20000315 (200018) EN C07D207-09
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6051593 A 20000418 (200026) A61K031-40
US 6114371 A 20000905 (200044) A01N043-38
US 6130238 A 20001010 (200052) A61K031-40
US 6133305 A 20001017 (200054) A61K031-40
ADT WO 9850356 A1 WO 1998-US9017 19980507; AU 9876842 A AU 1998-76842 19980507; EP 984930 A1 EP 1998-924746 19980507, WO 1998-US9017 19980507; US 6051593 A Provisional US 1997-50413 19970620, Provisional US 1997-59544 19970919, US 1998-99721 19980619; US 6114371 A Provisional US 1997-50977 19970620, Provisional US 1997-59384 19970919, CIP of US 1998-99842 19980619, US 1998-190970 19981112; US 6130238 A Provisional US 1997-50977 19970620, Provisional US 1997-59544 19970919, US 1998-99842 19980619; US 6133305 A Provisional US 1997-60194 19970926, US 1998-161046 19980925
FDT AU 9876842 A Based on WO 9850356; EP 984930 A1 Based on WO 9850356
PRAI US 1997-60194 19970926; US 1997-45838 19970507; US 1997-46868 19970508; US 1997-49324 19970611; US 1997-50412 19970620; US 1997-50413 19970620; US 1997-50977 19970620; US 1997-59336 19970919; US 1997-59381 19970919; US 1997-59384 19970919; US 1997-59544 19970919; US 1997-59677 19970919; US 1997-59971 19970925; US 1998-99721 19980619; US 1998-99842 19980619; US 1998-190970 19981112; US 1998-161046 19980925
IC ICM A01N043-38; A61K031-40; C07D207-09
ICS A61K031-415; A61K031-535; C07D209-04; C07D209-12; C07D209-34; C07D209-42; C07D211-02; C07D231-54; C07D307-02; C07D401-04; C07D403-06; C07D405-04; C07D413-04
AB WO 9850356 A UPAB: 19990203
Hetero- and carbo- arylidene indolin-2-ones, and their aza analogues, of formula (I) and their salts and prodrugs are new. A1-A4 = C or N, provided that, when any A is N, then the attached R is not present; Q = a mono- or bi- cyclic carbo- or heteroaryl system of formula (a)-(e): B1, B2 = C, N, O, or S; D1, E1, L1-L5 = C or N; D2, E2, J1 = N, O, or S; provided that any ring system (a)-(e) is already known in the chemical arts; J2-J4 = C, N, O or S; Z = O or S; R1 = H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, trihaloacetyl, hydroxy, alkoxy, acyl, acyloxy, COOR'', CONR18R19, CSNR18R19, guanyl, guanidyl, ureidyl, R''SO2, or trihalomethanesulphonyl; R'' = H, alkyl, cycloalkyl, aryl, or heteroaryl or heteroalicyclic (both bonded through a ring C); R2 = as R'', or halogen; R18, R19 = H, alkyl, cycloalkyl, aryl, acyl, trihaloacetyl, COOR'', R''SO2, trihalomethanesulphonyl, or C-peptidyl; or NR18R19 = 5 or 6 membered heteroalicyclyl; R3-R17, R81, R82, R91, R101, R111, R121 = H, alkyl, alkenyl, alkynyl, trihalomethyl, trihaloacetyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, alkoxy, alkylthio, aryloxy, arylthio, heteroaryloxy, heteroalicyclyloxy, R''SO, R''SO2, SO2NR18R19, R''SO2NR18, acyl, trihaloacyl, COOR'', acyloxy, CONR18R19, R19CONR18, cyano, nitro, halogen, OCONR18R19, R19CONR18, OCSNR18R19, R19CSNR18, phosphonyl, guanyl, guanidyl, ureidyl, trihalomethanesulphonyl, trihalomethanesulphonamido, amino, NR18R19, quaternary ammonium, W(CH2)mNR18R19, W(CH2)mC(=Y)T, N=CR18R19, NHR20, or VrM; R3-R6 can also = N-trihalomethanesulphonamido; or an adjacent two of R3-R6 = fused cycloalkyl, aryl, heteroaryl, heteroalicyclic, methylenedioxy, or ethylenedioxy; or R7R8 together, R8R81

together, and/or R81R82 together = 5 membered cycloalkyl, heteroaryl, or heteroalicyclic, or 6 membered cycloalkyl, aryl, heteroaryl, or heteroalicyclic; or R7, R8, and when any of R9-R12 = H, then the corresponding R91-R121 can also be hydroxy or thiol; or any pair of CR9R91 to CR12R121 = keto, or 5 or 6 membered spirocycloalkyl or spiroheteroalicyclic; W = N, O, or S; V = CRR', CR=CR', or C triple bond C; R, R' = H, alkyl, cycloalkyl, aryl, alkoxy, alkylthio, aryloxy, or halo; r = 1-10; M = a polar group; T = hydroxy, alkoxy, aryloxy, amino, N-hydroxyamino, R''COO, NR18R19, or N-peptidyl; m = 0-3; Y = O or S; R20 = up to 8C polyhydroxyalkyl; and n is defined elsewhere as 0 or 1. Alkyl, alkenyl and alkynyl are up to 20C, and cycloalkyl includes monocyclic and fused systems.

USE - (I) are protein kinase (PK) modulators, including the protein tyrosine kinases (PTK), both the receptor type EGF, HER-2, HER-3, HER-4, IR, IGF-1R, IRR, PDGFR alpha and beta , CSFIR, **C-Kit**, C-fms, Flk-1R, Flk-4, KDR/Flk-1, Flt-1, and FGFR- 1R to 4R; and non-receptor or cellular type Src, Frk, Btk, Csk, Abl, ZAP-70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk; or serine/threonine PTK, as are CDK-2 and Raf. (I) are useful in treatment of squamous cell carcinoma, astrocytoma, glioblastoma, melanoma, glioma, or cancers of the lung (including small cell), bladder, head, neck, breast, ovary, or prostate; diabetes, autoimmune or hyperproliferative or inflammatory disorders, or angiogenesis. The inflammatory disorders include rheumatoid arthritis, osteoarthritis, restenosis, fibrosis, psoriasis, endometriosis, atheroma, Alzheimer's disease, macular degeneration, hepatic cirrhosis, and haemangioma. Other applications are wound healing and prevention of embryo implantation.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B05-B01E; B06-H; B14-C09; B14-D06; B14-F02D; B14-G02D; B14-H01; B14-J01A4; B14-N03; B14-N12; B14-N14; **B14-N17C**; B14-S04

L83 ANSWER 12 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-531553 [45] WPIX
DNC C1998-159420
TI New pyrrolo-pyrimidine(s) - useful for treating proliferative and immune system diseases.
DC B02
IN ARNOLD, L; CALDERWOOD, D J; JOHNSTON, D N; MUNSCHAUER, R; RAFFERTY, P; TWIGGER, H L
PA (KNOL) KNOLL AG; (BADI) BASF AG
CYC 48
PI WO 9841525 A1 19980924 (199845)* EN 70p C07D487-04
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE
W: AL AU BG BR BY CA CN CZ GE HU ID IL JP KR KZ LT LV MX NO NZ PL RO RU SG SI SK TR UA US
AU 9868293 A 19981012 (199907) C07D487-04
NO 9904509 A 19990917 (200001) C07D000-00
US 6001839 A 19991214 (200005) C07D487-04
EP 970084 A1 20000112 (200008) EN C07D487-04
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT RO SE SI
CZ 9903283 A3 20000315 (200021) C07D487-04
BR 9808281 A 20000516 (200035) C07D487-04
SK 9901259 A3 20000516 (200036) C07D487-04
CN 1259950 A 20000712 (200054) C07D487-04
NZ 337529 A 20001027 (200062) C07D487-04
HU 2000001507 A2 20001030 (200064) C07D487-04
ADT WO 9841525 A1 WO 1998-EP1357 19980309; AU 9868293 A AU 1998-68293 19980309; NO 9904509 A WO 1998-EP1357 19980309, NO 1999-4509 19990917; US 6001839 A Provisional US 1997-40836 19970319, US 1998-42702 19980317; EP 970084 A1 EP 1998-913690 19980309, WO 1998-EP1357 19980309; CZ 9903283 A3 WO 1998-EP1357 19980309, CZ 1999-3283 19980309; BR 9808281 A BR 1998-8281 19980309, WO 1998-EP1357 19980309; SK 9901259 A3 WO 1998-EP1357 19980309, SK 1999-1259 19980309; CN 1259950 A CN 1998-805152 19980309; NZ 337529 A NZ 1998-337529 19980309, WO 1998-EP1357 19980309; HU 2000001507 A2 WO

1998-EP1357 19980309, HU 2000-1507 19980309
FDT AU 9868293 A Based on WO 9841525; EP 970084 A1 Based on WO 9841525; CZ 9903283 A3 Based on WO 9841525; BR 9808281 A Based on WO 9841525; NZ 337529 A Based on WO 9841525; HU 2000001507 A2 Based on WO 9841525
PRAI US 1997-40836 19970319; US 1998-42702 19980317
IC ICM C07D000-00; C07D487-04
ICS A61K031-505; A61P035-00
ICA A61P037-00
ICI C07D209:00, C07D239:00; C07D209:00, C07D239:00, C07D487-04; C07D209:00, C07D239:00, C07D487-04; C07D209:00, C07D239:00, C07D487-04
AB WO 9841525 A UPAB: 19981111
Pyrrolo[2,3-d] pyrimidines of formula (I) and their salts are new: R1 = H, 2-phenyl-1,3-dioxan-5-yl or 1-6C alkyl, 3-8C cycloalkyl, 5-7C cycloalkenyl or (optionally substituted phenyl) 1-6C alkyl (optionally substituted by one or more ORa, provided that ORa is not located on a carbon attached to nitrogen); Ra = H or 1-6C alkyl; R2 = H, 1-6C alkyl, 3-8C cycloalkyl, halo, OH, (optionally substituted phenyl) 1-6C alkyl, optionally substituted phenyl or R4; R3 = a group of formula (a) in which the phenyl ring is additionally optionally substituted; A = NH, O, NHSO2, SO2NH, 1-4C alkylene, NHCO, NHCO2, CONH, NHCONH, CO2 or S(O)p; or A is absent and R5 is attached directly to the phenyl ring; p = 0-2; R5 = optionally substituted phenyl and, additionally, when A is absent R5 = phthalimido optionally substituted by halo; or pyrazolylamino in which the pyrazole ring is optionally substituted by OH and/or optionally substituted phenyl; R4 = thienyl, benzo(b)thienyl, pyridyl, pyrazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl or indazolyl (all optionally substituted by 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, 1-6C alkylthio, OH, optionally substituted phenyl, (optionally substituted phenyl), 1-6C alkyl (optionally substituted phenyl) 1-6C alkylthio or (optionally substituted phenyl) 1-6C alkoxy); optionally substituted phenyl = phenyl optionally substituted by 1-6C alkyl, 1-6C alkoxy, phenoxy, OH, phenyl (1-6C) alkyl, halo, NR10R11, COR9, phthalimido (optionally substituted by halo), NO2 or the phenyl ring is benzofused forming naphthyl; R10, R11 = H, 1-6C alkyl, phenyl, 1-6C alkanoyl, 1-6C alkoxycarbonyl, 5-hydroxy-1-phenyl-3-pyrazolyl or benzoyl (optionally substituted by 1-6C alkyl, 1-6C alkoxy or halo); and R9 = OH, 1-6C alkoxy, phenoxy or NR10R11.
USE - (I) can be used for treating proliferative diseases and/or disorders of the immune system such as benign and neoplastic proliferative diseases (claimed). (I) are especially useful for treating autoimmune diseases, such as rheumatoid arthritis, thyroiditis, type 1 diabetes, multiple sclerosis, sarcoidosis, inflammatory bowel disease, myasthenia gravis and systemic lupus erythematosus; psoriasis, organ transplant rejection e.g. kidney rejection, graft versus host disease, benign and neoplastic proliferative diseases such as human lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and leukaemia, and diseases involving inappropriate vascularisation e.g. diabetic retinopathy, choroidal neovascularisation due to age-related macular degeneration and infantile hemangiomas. In addition, (I) may be useful in the treatment of disorders involving VEGF mediated oedema, ascites and exudats, including mascular oedema and adult respiratory distress syndrome. (I) may also be useful in the treatment of osteoporosis, Paget's disease, tumour-induced hypercalcaemia and bone metastases. (I) inhibit the kinase activity of **c-kit**, c-fms, EGFr, BCR, AbI, PDGFr, KDR/F/k-1, F/t-1, tie-1 and tie-2.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-D08; B14-C09B; B14-D06; B14-E10C; B14-H01; B14-K01; B14-N01; B14-N11; **B14-N17C**; B14-S01; B14-S04

L83 ANSWER 13 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-159160 [14] WPIX
DNC C1998-051310
TI Reducing or blocking atopic skin disease - using antagonist of activation of skin mast cells by corticotropin-releasing hormone.
DC B04 B05

IN THEOHARIDES, T C
PA (KOSP-N) KOS PHARM INC
CYC 22
PI WO 9805354 A2 19980212 (199814)* EN 19p A61K039-00
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA NZ
AU 9739089 A 19980225 (199829) A61K039-00
EP 942749 A2 19990922 (199943) EN A61K039-395
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6020305 A 20000201 (200013) A61K037-00
ADT WO 9805354 A2 WO 1997-US13776 19970806; AU 9739089 A AU 1997-39089 19970806; EP 942749 A2 EP 1997-936413 19970806, WO 1997-US13776 19970806; US 6020305 A US 1996-689277 19960806
FDT AU 9739089 A Based on WO 9805354; EP 942749 A2 Based on WO 9805354
PRAI US 1996-689277 19960806
IC ICM A61K037-00; A61K039-00; A61K039-395
ICS A61K031-00; A61K031-35; A61K031-495; A61K038-00; A61K038-17; A61K038-22
ICI A61K031:35, A61K031:495, A61K039-395
AB WO 9805354 A UPAB: 19980406
Reducing or blocking atopic skin disease (A), comprising administering an antagonist of the activation of skin mast cells by corticotropin-releasing hormone (CRH), is new. Also claimed are: (B) composition for skin disorders induced by CRH, comprising a CRH antagonist and carrier; (C) **kit** comprising, in separate compartments, antagonists of the degranulation effect of CRH on skin mast cells, i.e. inhibitor of binding of CRH to skin mast cell receptors, inhibitor of production or release of CRH in the skin, inhibitor of action of neurotensin on skin mast cells, inhibitor of production or release of neurotensin in the skin, inhibitor of production or action of somatostatin in skin mast cells, histamine-3 receptor antagonist, piperazine compound, hydroxyzine, bichromone and/or flavonoid; and (D) treating stress-exacerbated skin disorders or stress-exacerbated symptoms of an atopic skin disease, comprising topically administering a composition comprising a piperazine compound or its salt and a carrier.
USE - The method is used to treat stress-related skin disorders, e.g. eczema or urticaria.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-J06; **B14-N17**

L83 ANSWER 14 OF 14 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1993-368405 [46] WPIX
CR 1992-096822 [12]; 1999-457574 [38]
DNC C1993-163454
TI Compsn. contg. **C-kit** ligand and opt. haematopoietic factor - for treating e.g. leukaemia, anaemia, AIDS cancer etc., also its antagonists for treating allergies etc. and its anti-sense nucleic acid.
DC B04 D16
IN BESMER, P; BUCK, J; MOORE, M A; NOCKA, K
PA (SLOK) SLOAN KETTERING INST CANCER; (SLOK) SLOAN KETTERING INST CANCER
CYC 24
PI WO 9321936 A1 19931111 (199346)* EN 216p A61K035-16
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA HU JP KR RU US
AU 9341065 A 19931129 (199411) A61K035-16
EP 639979 A1 19950301 (199513) EN A61K035-16
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 07508721 W 19950928 (199547) 66p A61K038-00
EP 639979 A4 19961023 (199710) A61K035-16
AU 675429 B 19970206 (199714) A61K037-02
HU 70696 T 19951030 (199732) A61K035-16
US 5767074 A 19980616 (199831) A61K038-04
US 6001803 A 19991214 (200005) A61K038-04
ADT WO 9321936 A1 WO 1993-US3640 19930416; AU 9341065 A AU 1993-41065

19930416; EP 639979 A1 EP 1993-910645 19930416, WO 1993-US3640 19930416; JP 07508721 W JP 1993-519322 19930416, WO 1993-US3640 19930416; EP 639979 A4 EP 1993-910645 ; AU 675429 B AU 1993-41065 19930416; HU 70696 T WO 1993-US3644 19930416, HU 1994-3054 19930416; US 5767074 A CIP of US 1990-573483 19900827, CIP of US 1990-594306 19901005, CIP of WO 1991-US6130 19910827, Cont of US 1992-873962 19920423, US 1994-341456 19941117; US 6001803 A CIP of US 1992-873962 19920423, US 1994-325240 19941020

FDT AU 9341065 A Based on WO 9321936; EP 639979 A1 Based on WO 9321936; JP 07508721 W Based on WO 9321936; AU 675429 B Previous Publ. AU 9341065, Based on WO 9321936; HU 70696 T Based on WO 9321936

PRAI US 1992-873962 19920423

REP 3.Jnl.Ref; WO 9200376

IC ICM A61K035-16; A61K037-02; A61K038-00; A61K038-04
ICS A61K035-26; A61K037-66; A61K038-19; C07K007-10; C07K014-435; C07K014-52; C07K014-525; C07K014-535; C07K014-705; C07K015-06; C07K015-26; C12N015-12; C12N015-87

AB WO 9321936 A UPAB: 20000128
Pharmaceutical compsn. (A) contains (1) a **c-kit** (protooneogene) ligand (I) and (2) at least one haematopoietic factor () in a carrier.

Also new are (1) an antagonist (III) of (I) which is either a soluble, mutated (I) or a small molecule able to bind to the **C-kit** receptor but locking biological activity, (2) antisense nucleic acid (IV) able to bind to mRNA of (I), preventing its translation; (3) comspns. (A') consisting of (I) and a carrier, for ex vivo use, and (4) compsns. (A'') consisting only of (I) plus a carrier.

USE - (A) are useful for (1) improving engraftment of bone marrow transplants and bone marrow recovery after radiation etc. (HF is IL-1 and/or G-CSF); 92) treating acute or chronic myelogenous leukaemia (HF is GM-CSF or G-CSF); (3) treatment of leucopaenia (HF is G-CSF, GM-CSF or IL-3); (4) stimulation of progenitor cells (MF is at least one IL-1, IL-3, IL-6, GM-CSF, G-CSF or P(XY), or (5) increasing levels of stem cells in peripheral blood (HF is IL-7 or G-CSF).

Dwg.0/57

FS CPI

FA AB

MC CPI: B04-B03A; B04-B04F; B04-C01G; B12-A01; B12-A06; B12-D02; B12-D03; **B12-D07**; B12-G01; B12-G05; B12-G07; B12-J02; B12-J08; B12-K02; B12-K06; B12-L04; B12-L05; D05-H12

=> d his

(FILE 'HOME' ENTERED AT 08:52:02 ON 09 FEB 2001)
SET COST OFF

FILE 'MEDLINE' ENTERED AT 08:53:14 ON 09 FEB 2001

L1 1926 S STEM CELL FACTOR/CT,CN
L2 103629 S STEM CELLS+NT/CT
L3 1243 S PROTO-ONCOGENE PROTEIN C-KIT/CT,CN
L4 100775 S L1-L3 AND PY<=1999
L5 3090 S L4 AND C17.800./CT
L6 8114 S L4 AND A1.835./CT
L7 318 S L4 AND (MELANINS+NT OR MELANOCYTES+NT)/CT
L8 296 S L4 AND HYPERSENSITIVITY+NT/CT
L9 90 S L4 AND PIGMENTATION+NT/CT
L10 2454 S L1,L3 AND L4
L11 206 S L10 AND L5-L9
L12 9 S L11 AND HYPERPIGMENT?
L13 7 S L11 AND SKIN PIGMENTATION+NT/CT
L14 1292 S L10 AND (SIGNAL TRANSDUCTION+NT OR CELL COMMUNICATION+NT OR R
L15 1255 S L10 AND (D8. OR ENZYME ACTIVATION OR ENZYME STABILITY OR SUBS
L16 147 S L14,L15 AND L11
L17 146 S L12,L13,L16 NOT LONGLEY B?/AU

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L18          26 S L1/MAJ AND L17
L19          51 S L3/MAJ AND L17
L20        2675 S (STEM CELL FACTOR OR PROTO-ONCOGENE PROTEIN C-KIT)/CN
L21        1636 S (STEM CELL FACTOR OR PROTO-ONCOGENE PROTEIN C-KIT)/CT
L22        1039 S L20 NOT L21
L23          60 S L22 AND L17
L24         129 S L18,L19,L23
L25          17 S L17 NOT L24
L26      309128 S C17.800./CT
L27          58 S L26/MAJ AND L24,L25
L28      149446 S (A1.835. OR MELANOCYTES+NT OR MELANINS+NT)/CT
L29          58 S L28/MAJ AND L24,L25
L30         108 S L27,L29
L31          38 S L24,L25 NOT L30
L32          12 S L30 NOT AB/FA
L33       16060 S PIGMENTATION DISORDERS+NT/CT
L34        2362 S SKIN PIGMENTATION/CT
L35          32 S (L33/MAJ OR L34/MAJ) AND L30
L36           4 S L30 AND L33,L34 NOT L35
L37          72 S L30 NOT L33-L36
L38         104 S L35,L37
L39          11 S L38 NOT AB/FA
L40           9 S L12,L13 AND L38
L41           5 S L12,L13 NOT L40
                E MASTOCYTOSIS+ALL/CT
L42         109 S L38,L40,L41

    FILE 'BIOSIS' ENTERED AT 09:22:12 ON 09 FEB 2001
L43        4944 S SSCF OR SKIT OR STEM CELL FACTOR OR CKIT OR C KIT OR (PROTOON
L44        4449 S L43 AND PY<=1999
L45         291 S L44 AND *1850?/CC
L46          12 S L44 AND (HYPERPIGMENT? OR HYPER PIGMENT?)
L47         202 S L44 AND (MELANIN OR MELANOCYT?)
L48         200 S L44 AND ?INFLAM?
L49          99 S L44 AND 12508/CC
L50          21 S L48,L49 AND L45
L51           2 S L48,L49 AND L47
L52          10 S L46 AND L45
L53          32 S L46,L51,L52,L50
L54          28 S L53 NOT LONGLEY B?/AU
L55         105 S L44 AND ?PIGMENT?
L56          81 S L55 AND L45
L57          74 S L56 NOT LONGLEY B?/AU
L58          70 S L56 NOT L54
L59          12 S L58 AND (LIGAND OR UVB OR PIEBALDISM)/TI
L60          93 S L54,L59,L57
L61          23 S L60 AND 00520/CC
L62          22 S L60 AND CONFERENCE/DT
L63          70 S L60 NOT L61,L62
L64           1 S L63 AND SEMINAR/SO
L65          24 S L61,L62,L64
L66          69 S L60 NOT L65

    FILE 'BIOSIS' ENTERED AT 09:33:19 ON 09 FEB 2001

    FILE 'WPIX' ENTERED AT 09:36:21 ON 09 FEB 2001
L67         893 S L43
L68          46 S (B04-H16 OR C04-H16)/MC
L69         907 S L67,L68
L70          20 S L69 AND (B14-N17 OR C14-N17 OR B14-N17C OR C14-N17C OR B12-A0
L71          30 S L69 AND (P930 OR P940 OR P941 OR P942 OR P943 OR Q262)/M0,M1,
L72          24 S L69 AND (B14-C03 OR C14-C03 OR B12-D07 OR C12-D07)/MC
L73          47 S L70-L72
L74          46 S L73 NOT LONGLEY B?/AU
L75          10 S L74 AND L68
L76          30 S L74 AND STEM CELL FACTOR
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L77           0 S L74 AND PROTO ONCOGENE
L78          15 S L74 AND (CKIT OR C KIT)
L79          46 S L75,L76,L78
L80          30 S L79 AND STEM CELL FACTOR
L81          10 S L79 AND L68
L82          32 S L80,L81
L83          14 S L79 NOT L82

     FILE 'WPIX' ENTERED AT 09:49:41 ON 09 FEB 2001
           SET COST ON
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